SCIENCE

9 August 1957

Volume 126, Number 3267

Editorial Research and Political Power 237

Articles The Genetic Hazards of Nuclear Radiations: *B. Glass* 241

W. Bothe, Experimental Nuclear Physicist: *H. Maier-Leibnitz* 246

News of Science News Articles and Briefs; Scientists in the News; Recent Deaths 248

Reports Nature of Solvent Transfer in Osmosis: *A. Mauro* 252

Aggressive Behavior in Castrated Starlings: *D. E. Davis* 253

Nature of Fluorophore Localizing in Tetracycline-Treated Mouse Tumor: *T. L. Loo, E. D. Titus, D. P. Rall* 253

Prevention of Toxicity of Amethopterin for Sarcoma-180 Cells in Tissue Culture: *M. T. Hakala* 255

Gastric Secretagogue Effect of Lysine Monohydrochloride: *A. M. Sackler* and *L. H. Sophian* 255

Delayed Pain as a Peripheral Sensory Pathway: *B. Libet; M. H. Jones* 256

An *in vitro* Effect of Vitamin D on Citrate Oxidation by Kidney Mitochondria: *H. F. De Luca* and *H. Steenbock* 258

Insect Nutrition and Metabolism of Sterols: *S. D. Beck* and *G. G. Kapadia* 258

Cytolysis versus Differentiation in Antineurula Serum: *G. W. Nace* and *K. Inoue* 259

Thermal Protection of Choline Chloride from Decomposition by Ionizing Radiation: *I. Serlin* 261

Segregation of Plasmagenes and the Determination Problem: *P. Michaelis* and *F. Bartels* 261

Role of Fumarate in Formation of Stromata in "Vernalized" Ergot Fungus: *A. St. Garay* 263

Conditioned Inhibition of Respiration and Heart Rate in the Goldfish: *L. S. Otis, J. A. Cerf, G. J. Thomas* 263

Book Reviews *Selected Papers in Statistics and Probability by Abraham Wald; The Water Relations of Terrestrial Arthropods; Nonparametric Statistics for the Behavioral Sciences; Advances in Cancer Research; Separation and Purification; High Energy Accelerators; Early Electrical Machines; Ernest Rutherford, Atom Pioneer; Progress in the Chemistry of Organic Natural Products;* New Books; Miscellaneous Publications 265

Meetings and Societies Mathematics Instruction; Meeting Notes; Forthcoming Events 270

Equipment News 275

MERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Sargent Constant Temperature Bath

The 0.01° C. Sargent Constant Temperature Water Bath, which is employed in many laboratories throughout the world where a precise, reliable thermostat is required, is now being supplied with an improved relay unit and heating system. The central heating and circulating unit of the bath is now equipped with three cylindrical heating elements rated at 200, 300 and 400 watts respectively. The 200 watt heater is controlled by the No. 81835 mercurial thermoregulator through a thyratron tube and saturable core reactor in the relay unit. (The use of a saturable core reactor obviates the difficulties commonly encountered with mechanical relaying systems such as pitted contacts, broken moving parts and freezing.) By means of a control mounted on the panel of the relay the output of this heater can be varied from the full 200 watts to approximately 60 watts, thus permitting such adjustment of the heater output that positive overshooting of the regulatory temperature is minimized. With the improved relay system this bath can be adjusted to a precision of ±.005° C. when operating in the vicinity of 25° C.

An autotransformer, adjusted by means of a knob on the relay unit panel, permits the setting of the 300 watt heater so that heat loss from the bath is almost compensated and negative overshoot is reduced to a negligible quantity.

The 400 watt heater may be used to quickly raise the bath temperature to the desired operating level or, in the case where sacrifice of some precision of regulation is of no consequence, to permit operation of the bath at temperatures above 60° C.

In addition, the relay unit is equipped with a master switch, a switch for each heater and a pilot light to indicate that the circuit to the 200 watt heater is closed. Maximum power consumption 1100 watts.

S-84805 WATER BATH—Constant Temperature, 0.01° C., Sargent. Complete with Pyrex jar, 16 inches in diameter and 10 inches in height; central heating and circulating unit; constant level device; cooling coil; No. 81835 thermoregulator and relay unit with cord and plug for connection to standard outlets. For operation from 115 volt 50/60 cycle circuits **$300.00**

S-81991 TUBE—Thyratron, Type 2050. Each ..... **$ 4.40**

S-81992 LAMP—Neon Pilot Light. Each.... **$ 1.00**

S-84845 VESSEL—Water Bath Jar, PYREX Brand Glass. Each..... **$44.00**

SARGENT *SCIENTIFIC LABORATORY INSTRUMENTS • APPARATUS • SUPPLIES • CHEMICALS*

E. H. SARGENT & COMPANY, 4647 W. FOSTER AVE., CHICAGO 30, ILLINOIS
MICHIGAN DIVISION, 8560 WEST CHICAGO AVENUE, DETROIT 4, MICHIGAN
SOUTHWESTERN DIVISION, 5915 PEELER STREET, DALLAS 35, TEXAS
SOUTHEASTERN DIVISION, 3125 SEVENTH AVE., N., BIRMINGHAM 4, ALA.

SCIENCE is published weekly by the AAAS, 1515 Massachusetts Ave., NW, Washington 5, D.C. Entered at the Lancaster, Pa., Post Office as second class matter under the act of 3 March 1879. Annual subscriptions: $7.50; foreign postage, $1; Canadian postage, 50¢.

9 August 1957, Volume 126, Number 3267

SCIENCE

SCIENCE, founded in 1880, is published each Friday by the American Association for the Advancement of Science at Business Press, Lancaster, Pa. Entered at the Lancaster, Pa., Post Office as second class matter under the Act of 3 March 1879.

SCIENCE is indexed in the *Reader's Guide to Periodical Literature* and in the *Industrial Arts Index*.

Editorial and personnel-placement correspondence should be addressed to SCIENCE, 1515 Massachusetts Ave., NW, Washington 5, D.C. Manuscripts should be typed with double spacing and submitted in duplicate. The AAAS assumes no responsibility for the safety of manuscripts or for the opinions expressed by contributors. For detailed suggestions on the preparation of manuscripts, book reviews, and illustrations, see *Science* 125, 16 (4 Jan. 1957).

Display-advertising correspondence should be addressed to SCIENCE, Room 740, 11 West 42 St., New York 36, N.Y.

Change of address notification should be sent to 1515 Massachusetts Ave., NW, Washington 5, D.C., 4 weeks in advance. If possible, furnish an address stencil label from a recent issue. Be sure to give both old and new addresses, including zone numbers, if any.

Annual subscriptions: $7.50; foreign postage, $1; Canadian postage, 50¢. Single copies, 25¢. Special rates to members of the AAAS. Cable address: Advancesci, Washington.

Rates effective 1 January 1958: $8.50; foreign postage, $1.50; Canadian postage, 75¢. Single copies, 25¢.

Research and Political Power

It is now widely accepted that research is the spearhead of the economic growth of a country, giving rise to new products, new industries, and new jobs. Over the last two decades, the pattern of industry of the more highly developed nations has altered massively in accordance with world scientific discovery, and increasingly countries and firms are concerning themselves with how much of their income they should invest in research.

This does not mean that economic strength is determined by the research expenditure of a nation or a corporation. Many other factors operate—availability of raw materials, investment capital, skilled manpower, and, perhaps above all, leadership. It is probably true, however, that the greatest economic gain comes to those countries which exploit research most quickly and most completely, rather than to those which contribute most to the world store of new knowledge.

This is especially so since it is still accepted throughout the world that the results of fundamental research should be published freely and internationally. The pool of common world knowledge is therefore there for all to exploit who will and can. It is frequently said that, until World War II, at any rate, the United States had the genius to exploit new discoveries more quickly than other nations, while the countries of Western Europe produced new science to a greater extent than other regions but failed to make full use of it. There is certainly much truth in this, but as science and industry become more complicated, exploitation and research contribution are tending to come ever closer together.

The fact is that very little of contemporary discovery in fundamental research can be put to productive use until much applied research has been undertaken. Fundamental research, applied research, technological development, and production are becoming more and more parts of the same spectrum of activity in the new science-based world into which mankind is emerging. This means that research power in the larger sense will, in the future, be more determinative of economic power.

While the economic significance of research has long been accepted, albeit in some places grudgingly, it is only recently that its political influence has become obvious. The atomic and hydrogen bombs dominate the foreign policies of the powers that possess them and influence greatly the foreign policies of countries which lack them. But even neglecting these scientific monsters, whether they are regarded as threats to the peace or as deterrents to war, modern warfare and defense have become so sophisticated in the technological sense with the numerous uses of radar, jet planes, guided weapons, proximity fuses, and so forth, that only countries possessing highly developed research resources and the elaborate industries supporting the defense program can feel secure and strong.

Political power is founded on economic and defense strength, both of which are increasingly dependent on research. It follows, therefore, that research power and political strength are now mutually dependent through a complex chain of cause and effect. This is recognized even by the politicians. In introducing a recent debate on foreign affairs in the House of Commons, Harold Macmillan, the British prime minister, said, "The

(*Continued on page 238*)

scientist is always ahead of the politician." Scientific discovery has now an immediate and profound effect on foreign policy.

Research has always required the support of a patron. In the early days of the experimental method, the individual scholar often sought the support of the prince or man of wealth just as did Mozart and Hayden. Later, as the possible "uses" of research became recognized and needs became greater—also, one might add, as princes and millionaires became scarcer—patronage was taken over by industry and the state. It was not, however, until World War I that this became marked.

Germany was the first of the great powers to encourage and exploit science. The rise of German political power and scientific achievement followed the political unification of that country, a phenomenon which might easily be repeated if Europe as a whole now achieves a degree of political or at least economic unity. It is unlikely that Germany could have waged World War I, or at any rate have fought for a prolonged period, but for the practical method of nitrogen fixation, devised by Haber, and the chemical industry which applied it. Equally, on the other side, this war having proved itself, although by later standards only relatively, to be a scientific war, the British quickly discovered their lack of scientific resources and proceeded to build them up quickly. The rise of the very active British chemical industry received a great impetus from this, and on the Government side, the Department of Scientific and Industrial Research was created, as well as the first of the industrial research associations.

Until the outbreak of World War II, the concentration of research power was at least on the fundamental level in Western Europe, especially in the laboratories of Germany, Great Britain, Scandinavia, the Netherlands, and Switzerland. It is probable that this area was producing as much as 70 percent of the world's significant scientific output, although American science, particularly industrial research, was building up quickly during this time. The political strength of Western Europe during the same period was very great.

During and after World War II, great changes took place in the distribution of political power. The U.S.S.R. grew greatly in importance, Germany was defeated, while the political force of the rest of Western Europe, exhausted by war or occupation, declined considerably. At the same time, the United States developed to become the strongest world power. Research power too followed this trend. The total volume of scientific activity has increased everywhere, to a large extent because of direct or indirect government finance, and it has been exaggerated by continued defense preparations and atomic energy programs. Relatively, both with respect to pure and applied research, the scientific activity of the United States has soared in volume. Ewell has calculated that, of the cumulative total of money spent on research and development from the Declaration of Independence until the end of 1954, 45 percent was spent in the last 5 years of the period.

For the first time also, the U.S.S.R. has become a major force in science, and her acceleration, although starting at a much lower level, probably exceeds that of the United States. In Western Europe, there has been a great and healthy growth of scientific activity. The British atomic energy and aeronautical programs, for example, have been outstandingly successful. Germany has also made a remarkable scientific recovery since the war. It is clear too that in Europe there has been a substantial increase of facilities for the quick development and exploitation of scientific discovery. Nevertheless, the proportion of world research product coming from Western European laboratories has fallen greatly with the expansion of resources in the United States and the U.S.S.R, and this is in parallel with the declining political strength of the area.

It is difficult to give a quantitative estimate of these trends. It would be useful if some enterprising operational research scientist would analyze by region the number of scientific papers in the main abstract journals for, say, 1938, 1950, and 1956. It would probably emerge that Western Europe's share of research output had fallen from a prewar figure around 70 percent of the world total to below 40 percent of the much bigger amount today. With the impressively large Soviet effort in the training of scientists and technologists, we may expect the relative research effort of the U.S.S.R. to mushroom within the next 10 years, and by the end of that period, China and the other populous countries of the East will be occupied with research in a big way. Already the training of scientists and the creation of research laboratories is proceeding rapidly. Many interesting Chinese papers are now appearing in the Soviet abstract journals.

There is no evidence that scientific ability or even genius is the monopoly of any country or race. Indeed, it may well be that potential ability is spread throughout the human population more or less with a statistical uniformity, although, of course, opportunities to actualize it vary greatly on account of nutrition, environment, economic level, and educational possibilities. If these human potentialities were developed fully and research were spread uniformly throughout the world, the proportion done by the United States would be about 6 percent and that by Western Europe about 9 percent of the total. It is certainly not to be expected that this will happen, at least for many years to come, but nevertheless the drive to improve economic standards throughout the world and particularly the spectacular building up of educational and research resources behind the Iron Curtain is bound to produce shifts in that direction.

It takes 5 to 10 or more years for the results of fundamental research to develop economically in the form of new materials, instruments, or production methods, so that the next decade should see in full measure the fruits of the great upsurge of American science since the war, followed closely by that of the U.S.S.R. and later by China. The figures hazarded here may be inaccurate, but the relationship between research, political, and economic power is now so close that these undeniable trends command consideration by those who are concerned with scientific and educational policy.

As the total amount of research undertaken in different parts of the world increases, individual countries will become progressively less self-sufficient and will have to draw heavily on work undertaken abroad. With the open publication of research, this is at present outwardly the case. In reality, however, there is a great deal of unconscious and understandable nationalism amongst scientists. Journals published in one's own country are much more widely accessible than those from abroad, and this is enough to insure that domestic research results are read more quickly and more widely than those from abroad. Beyond this, language difficulties have a similar effect. It is doubtful whether more than a very small percentage of the results of Soviet research are yet used by the scientists of the United States or Western Europe. On the other hand, the U.S.S.R. and the satellite countries with their strong and centralized information services have a deliberate policy of full exploitation of world research. In the West, we are as yet hardly aware of the magnitude of this problem and have certainly not tackled it seriously.

ALEXANDER KING
European Productivity Agency, Paris, France

Kodak reports on:

film for cases where no other film will do . . . cellulose acetate phthalate in the tummy . . . 25 years in the commercial plastics business

For your own good

It is now possible to walk up to an ordinary film counter and buy a roll of 120 or 620 roll-film that is just too fast for your own good. We do *not* recommend the new *Kodak Royal-X Pan Film*, except for special cases involving very poor light conditions, very high shutter speeds, or very small lens openings. Processing it by current commercial photofinishing techniques will lead to unsatisfactory results; instead, one must follow the special processing instructions packed with the film. Measured by the official ASA method, the Exposure Index is 650, but we think you will get along better handling it on the assumption of a 1600 exposure index.

17 years have gone by

The great Ivan Pavlov—he of the salivating dogs that you learned about in Psychology 1—did more than found behaviorism. By shedding illumination into the dark workings of the alimentary canal, the old boy lit the light that set off a chain of more than 100 patents on preparations that would get medicines safely through the stomach and on into the intestine. Each shines forth, lives out its allotted legal span of 17 years with more or less success, expires, and becomes part of the art that anyone skilled in the art of pharmacy may freely practice.

This year expiration befell U. S. 2,196,768, one of the more successful of them. It belonged to us, of all people.

In the dull monotone affected by the patent bar, this document drones on and on about "a medicament surrounded by an enteric film or layer of a cellulose derivative which contains a dicarboxylic acid radicle [*sic*] and which contains free carboxyl groups . . . " etc., etc., etc. In Examples VII and VIII and Claim 10 appears cellulose acetate-phthalate. That was it. That is our baby.

Reports in the pharmaceutical journals over the years on experiments to compare the properties of available enteric coating materials usually wind up reading like testimonials for CAP. Well over a billion doses of medicine coated with CAP have been swallowed. That may not be so many for 17 years, but it isn't bad either.

The reason CAP has been able to do mankind a little good is that it's just extremely resistant to gastric action, most susceptible to the hydrolytic influence of intestinal esterases, and quite independent of the assumption that the contents of the human upper intestine are reliably alkaline. Also, of the controversial assumption that the stomach empties at a reliable rate. Tablets coated with CAP have shown no signs of disintegration after seven days in a continuously agitated artificial gastric juice. In the same investigation in simulated intestinal juice at pH 6.9, rupture took place in 70 to 75 minutes, while at pH 8.5 all tablets disintegrated within 50 minutes.

The bill for the cellulose ester research that led to CAP has been paid. Now if you want to make an enteric-coated medicament with it, your lawyers can forget about our lawyers. All we can do is hope you will buy Eastman *Cellulose Acetate Phthalate, wherein about half of the original glucose hydroxyl groups are acetylated and about a quarter are phthalylated with one of the two carboxyls of phthalic acid. It is sold by Distillation Products Industries, Rochester 3, N. Y. (Division of Eastman Kodak Company) and looks like this:*

Hooray!

This fall we celebrate the 25th anniversary of our entry into commercial plastics (as distinguished from plastics for photographic film base, which we have been in since 1889). Hooray.

If you share our elation over the occasion, you will permit us to send you a plastic (*Tenite Butyrate*) commemorative medallion depicting one of the first U. S. injection molding machines. This heraldic device marks the historic fact that injection molding of plastics became an art of mankind through our exploitation of the discovery that cellulose acetate, mixed with a plasticizer, could be squirted hot. Hooray!

For sophisticates who look beyond butyrate medallions for their excitement, our plastics story has a slant that even they may find stimulating. That's the part where we mention psychophysics, profess our disdain for color standards in the plastics trade, and irritate our competitors by enthusiastically pushing the idea of custom colors.

The joy that the human race takes in its color vision has brought us prosperity.

Long live *Kodachrome*, *Kodacolor*, *Ektachrome*, *Ektacolor*, and *Eastman Color Films!* Also *Chromspun Acetate Yarn!*

The chromaticity diagram of the International Commission on Illumination—long may it wave!

Long live those gallant fellows of ours who spend their 8-to-5 lives exploring its mathematical properties and conclude that the normal eye is capable of about two million distinguishably different color sensations, half of which are possible as colors of actual objects!

Long live the independently wealthy automotive genius who decides just how much difference from any of the 38,000 extant colors in sturdy *Tenite Acetate*, extra tough *Tenite Butyrate*, and warmly soft *Tenite Polyethylene* it will take to create a certain effect in your wife's mind when she sneaks a peek into the 1959 model while waiting around in the showroom for the service department to make its estimate on overhauling the old heap!

For a reprint of a very recent paper of ours that tells how to build an electronic digital tristimulus integrator that attaches to a recording spectrophotometer and reads off ICI co-ordinates for any color, write Eastman Kodak Company, Research Laboratories, Rochester 4, N. Y. For the commemorative medallion, or for any conceivable color effect in Tenite Plastics, *which are, frankly, the aristocratic family of the plastics age, write Eastman Chemical Products, Inc., Kingsport, Tenn. (Subsidiary of Eastman Kodak Company).*

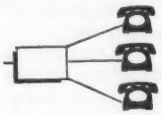
Kodak
TRADEMARK

This is another advertisement where Eastman Kodak Company probes at random for mutual interests and occasionally a little revenue from those whose work has something to do with science

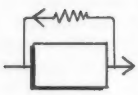
Pacemakers in the technology of our electronic age

Certain discoveries, inventions and developments of Bell Telephone Laboratories have been truly epochal in their effect upon the technology of our time. Each has come out of a single quest—a search for ways to make telephony ever better. But many have opened the way to exciting advances in TV, movies, radio, horology, astronomy. Here are ten of Bell Laboratories' contributions to the modern world.

Electronic amplifier. First high-vacuum electronic amplifier. Made possible long distance telephony and then opened the way to radio broadcasting.



Wave filter. Precisely separates bands of frequencies. Provided major key to economical sharing of the same wires by many voices or radio programs. Indispensable control tool in radio, television and radar.



Negative feedback amplifier. Provides distortionless and stable amplification. Made possible the enormous, precisely controlled amplification needed in long distance telephone calls. The principle is now basic in high-quality amplifiers for radio, TV and high-fidelity reproduction.

Quartz crystal. Standard super-accurate quartz-crystal oscillator developed for frequency controls in radio telephony. Has also become the standard control for clocks in world's astronomical laboratories.

Coaxial cable system. Hollow tube with a central conductor was developed to transmit hundreds of voices simultaneously. Now also provides long distance carrier for TV in partnership with microwave beams.

Transistor. Tiny solid-state device uses extremely small amounts of power to amplify signals. Makes possible electronic telephone switching and much smaller hearing aids, radios, TV sets and electronic computers.

Dial system "brain and memory." Takes over your call and sees that you are connected in the best and quickest way. Newest example: Direct Distance Dialing from home telephones to any part of the nation.

Waveguide. Hollow conductor transmits high-frequency waves. From this came the "pipe" circuits that are essential to radar and very short-wave radio communications.

Microwaves. Bell Laboratories developed long distance microwave transmission. It operates by focusing radio beams from station to station, carries cross-country telephony and TV.

Radio astronomy. This great new science began in the study of radio interference at Bell Laboratories . . . with the tremendous discovery that radio waves emanate from the stars.

BELL TELEPHONE LABORATORIES

WORLD CENTER OF COMMUNICATIONS RESEARCH AND DEVELOPMENT

9 August 1957, Volume 126, Number 3267 SCIENCE

The Genetic Hazards of Nuclear Radiations

Bentley Glass

Since the years 1927 and 1928, when Hermann J. Muller (*1*) and Lewis J. Stadler (*2*) independently discovered that x-rays will produce permanent hereditary alterations in animals and plants, respectively, the induction of mutations by ionizing radiations and the study of the changes brought about has become a major subscience of genetics. Hundreds of investigators have contributed to our present knowledge of radiation-induced mutation, and the full gamut of organisms, from viruses to flowering plants and mammals, has been found to be similarly susceptible. Meanwhile, great advances were also made in the cytological and biochemical analyses of the hereditary material, and today these approaches to an understanding of the intrinsic nature of mutations have come to a common focus. Our major question may then be phrased: How does radiation bring about permanent alterations of the hereditary material, and what kinds of changes are induced?

Chemical Nature of Hereditary Material

According to the overwhelming weight of present evidence, genetic information is transmitted from generation to generation in all organisms, sexual and asexual alike, through the chemical medium of deoxyribose nucleic acid or, in certain viruses, by another form of nucleic acid. The chromosomes, which have been demonstrated by genetic experiments to carry the units of heredity, the genes, are made up chiefly of deoxyribose nucleic acid and a basic protein, commonly a histone, together with some ribose nucleic acid and a small amount of nonbasic protein. The ribose nucleic acid, which is even more abundant in the nucleolus and the cytoplasm of cells than in the chromosomes, is thought to convey the chemically coded information from the nucleus to the sites of protein synthesis in the cytoplasm; but, except in certain viruses, it can hardly constitute the primary code itself.

Protein used to be thought the only substance of sufficient chemical complexity to be able to serve as the basis of heredity; but the advancing knowledge of the nucleic acids has revealed that they are equally capable of forming a virtually illimitable chemical code of information, through variations in the sequence of the four organic bases found in each polynucleotide; and the fact that the histone of the chromosomes in some species becomes completely replaced in the spermatozoa by an even simpler, more basic protamine seems to exclude the possibility that the protein of the chromosomes is the primary hereditary material. The evidence that the hereditary characteristics of *Pneumococcus* strains may be permanently transformed by subjecting recipient cells to the highly purified, extracted deoxyribose nucleic acid from donor cells of a different type, together with reconstitution experiments with tobacco mosaic virus, lend overwhelming weight to the view that nucleic acid, and generally deoxyribose nucleic acid, is the primary hereditary material.

In these reconstitution experiments, performed by Fraenkel-Conrat and others, the ribose nucleic acid core of one species of virus has been reenclosed in the protein coat of another. In each case, the infectivity and virtually all other hereditary properties of the reconstituted virus are those characteristic of the species that supplied its ribose nucleic acid, and not those of the species that supplied its protein (*3*).

We thus arrive at the view that the two purines of deoxyribose nucleic acid (adenine and guanine) and the two pyrimidines (thymine and cytosine) must in their seriation along the polynucleotide spell out the hereditary code, for the backbone of the polynucleotide, composed of deoxyribose units linked by phosphate groups to form a long chain, is similar in chemical structure throughout the length of the molecule. It is still quite uncertain how many nucleotides commonly comprise a gene, and whether the genes are separated by protein material or metal-ion bonds, or whether the genes are contiguous, or even overlap. But one must begin to think of mutations, at any rate, in terms of the chemical nature of the hereditary material and its sequences of bases. A mutation is some alteration in this material which, when chromosomes reproduce themselves, is itself replicated, and thus is transmissible in mitotic and meiotic cell divisions.

Chromosomal Mutations

Genetically detected mutations following exposure to ionizing radiations may involve microscopically visible alterations of the chromosomes or may be submicroscopic in character. The gross chromosomal aberrations, as is well known, include reciprocal shifts of segments between chromosomes, inversions of segments within a single chromosome, deficiencies arising by deletion of a segment, and duplications of a segment. In all these types of chromosomal mutation, it is easy to see that chromosomes have been fractured by the radiation and that their broken ends have been reunited in some new pattern. In each case, at least two breaks must have occurred within the same nucleus in order to permit the

The author is professor of biology at Johns Hopkins University, Baltimore, Md. This article is based on papers that were presented at a symposium on Genetics and Radiation Hazards held in Washington, D.C., by the National Academy of Sciences, 22 Apr. 1957, and at the Inter-American Symposium on the Peaceful Application of Nuclear Energy, Brookhaven National Laboratory, 16 May 1957.

rearrangement, and it is therefore not surprising to learn that the frequency of such mutations increases as the square, or some higher power, of the dose.

At low dosages, such mutations are therefore very rare, since they involve the coincidence of two or more effective "hits" within the same nucleus. True, there are also single breaks which invariably lead to the loss of terminal parts of chromosomes, in case they do not heal together again (that is, "restitute"). But these, like the internal deficiencies, are invariably very harmful unless they are extremely small, at the lower limit of cytological visibility. They are consequently rapidly eliminated after a few cell generations or can only be kept for experimental study by great effort and ingenuity. They are, in other words, of a dominant lethal nature.

Translocations (except in certain plant species) may be described as commonly semisterile in effect; often they lower the viability of their carriers as well. Only the inversions and smaller duplications are in general sufficiently harmless to be transmitted in natural populations and to play a part in the evolutionary changes of species (*4*).

It is a striking fact that, in animals which have been used for studies of radiation-induced mutation, the male germ cells during meiosis, and especially during spermiogenesis, seem far more sensitive to the radiation than immature male germ cells (spermatogonia) or female germ cells of any stage (*5*). Inasmuch as the chromosomal mutations are produced chiefly by high doses, and in those very cells that are most readily eliminated through the production of the well-known temporary sterilization of the male after acute doses of radiation, there is relatively little genetic damage to be expected from them.

Point Mutations

Of chief importance, then, are the point mutations, in which the lesions in the hereditary material are submicroscopic in size. Submicroscopic mutations must be basically of a similar nature to the gross, cytologically visible mutations —that is, they presumably consist of alterations in the sequence of purine and pyrimidine bases, through inversions of segments, insertions, deletions, and substitutions.

All existing genetic evidence indicates that the frequency of point mutations increases linearly with the radiation dosage (Fig. 1). In studies of *Drosophila*, this has been demonstrated to hold over the dose range from 25 up to 6000 roentgens (*6*). In some plants, the linear range has been extended down to about 5 roentgens. In mice, the linearity in relation to dose holds over the range from 300 to 600 roentgens, but there is no sign that it does not hold below that range (*7*).

This linear proportionality to the dose, over and above the spontaneous frequency of mutation, implies two things: (i) as long as dosage is measured in terms of roentgens (that is, in terms of the ionization produced by the radiation) absorbed quanta are individually effective, and it does not take two or more to produce a mutation; and (ii) there is no sign of a threshold dose below which mutations are not produced, but rather, even the lowest doses are proportionally mutagenic, and all doses, however distributed, are additive or cumulative in effect. It also follows that, under normal conditions, the intensity with which the dose is given, whether in a short time at high intensity or over a long period at low intensity, whether given uninterruptedly or in fractions separated by rest periods, makes no difference.

Finally, these relations are also borne out by the evidence that differences in the energy of quanta are not significant with respect to mutation. Whether the quanta are the extremely powerful ones of cosmic rays or the less energetic ones of gamma radiation or x-rays, down to the weakest ionizing quanta of the grenz-rays, the mutational effect remains linearly proportional to the ionization produced. Ionizing particles, such as beta-rays (electrons), alpha-particles, and neutrons are also effective in producing mutations, both of the chromosomal and of the submicroscopic sort. They show differences in efficiency because of the differences in the ion density along the tracks of the various types of particles and consequently the differences in probability that one particle may produce more than a single lesion in a chromosome; but the dosage relation for the point mutations is in each case one of linear proportionality.

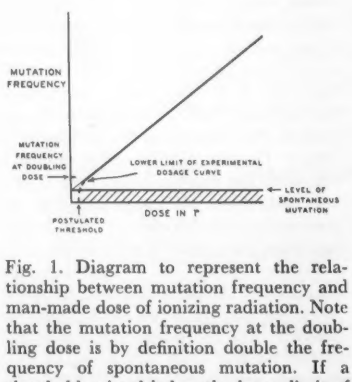


Fig. 1. Diagram to represent the relationship between mutation frequency and man-made dose of ionizing radiation. Note that the mutation frequency at the doubling dose is by definition double the frequency of spontaneous mutation. If a threshold existed below the lower limit of the experimentally demonstrated linear portion of the dosage curve, the curve would have to follow the heavy dotted line. This would imply that the lowest applied doses produced no mutations, and then a short region of increasing dose would yield mutations with an efficiency significantly exceeding that of the long linear portion of the dosage curve. For physical reasons this is very improbable. If any considerable portion of the spontaneous mutation is, for a particular species, induced by the background radiation, the entire curve, including the origin, would be shifted correspondingly to the right if the natural radiation were included with the applied radiation in the definition of dose. If the background radiation is not included in the dose, the curve and its origin would be unaltered.

Indirect Action

The direct proportionality of mutation frequency to dose does not mean, however, that the high-energy quantum must score a direct "hit" on the deoxyribose nucleic acid of the chromosomes to bring about a mutation. Indirect action is not excluded, provided that the genetic effect is proportional to the ionization produced by the radiation. The effectiveness of chemical mutagens in producing mutations and the alteration of the efficiency of x-rays in producing mutations by modification of the oxygen concentration in the tissues demonstrate sufficiently that indirect, chemical steps may intervene—perhaps always intervene—between the ionization and the mutation. For example, in an atmosphere of oxygen, a dose of 2000 roentgens produces more mutations than it does in an atmosphere of air; and when it is delivered in nitrogen or helium, the frequency of mutations is diminished.

Moreover, a recent study by A. M. Clark of Australia (*8*) demonstrates an effect of the intensity at which the radiation is delivered if the x-rayed spermatozoa are simultaneously subjected to the action of sodium azide. Almost twice as many sex-linked recessive lethal mutations were produced at an intensity of 2000 roentgens per minute as at 100 roentgens per minute. This is taken to mean that chemical mutagens produced by the radiation, and sensitive to the action of azide, can accumulate to higher concentrations when the dose rate is very high, and consequently stand a better chance of producing mutations after diffusing to other points within the nucleus.

This type of finding raises once again the problematical existence of a threshold below which the intensity of the radiation—and consequently the concentration of chemical agents produced by it—is too low to bring about mutations. Under certain conditions, this may ulti-

mately turn out to be the case. However, it should be stressed that under ordinary conditions and with low to moderate dose rates, the linear proportionality and the nonexistence of a threshold appear to obtain. Until we are assured to the contrary, the only safe working assumption is that every dose, even the lowest, is effective in producing mutations and is consequently genetically damaging.

Somatic Cells

It would be a grave mistake to think that mutations of the hereditary material are confined to the reproductive cells, or germ line. They can presumably occur also in the somatic cells of any tissue. At the present time, however, we have all too little knowledge of what happens to mutant somatic cells. Sometimes these cells exhibit a mutant phenotype, and a mosaic individual results. More significant would be dominant or partially dominant effects on essential metabolic and biochemical processes, which might consequently be impaired.

Recent studies by E. B. Lewis of the origin of leukemia (*9*) and by G. Failla of the phenomenon of aging (*10*) suggest that because both of these, like radiation-induced mutations, seem to increase linearly with the dose of ionizing radiation and without sign of a threshold, they too may result from the induction of mutations by radiation and their accumulation in somatic cells. Possibly cancer, in general, may arise through the same cumulative effect, which does not at all exclude the intervention of other types of agents (viruses, nutritive factors, and chemical agents) in the final outburst of malignant growth.

Thus, in some of my own experimental studies with certain strains of *Drosophila*, the induction of two distinct forms of abnormal growth may be initiated either by ionizing radiation or by excessive amounts of tryptophan in the diet (*11*). The genetic basis of the effect comprises, in each case, a mutant gene responsible for the abnormal growth and a suppressor gene that under ordinary circumstances inhibits it. By a moderate dose of radiation (1000 roentgens)—moderate for *Drosophila*—or by alteration of the diet, the effectiveness of the suppressor is destroyed—in this instance by interference with its action, and not by mutation. Thus, radiation or dietary factors may so upset a balanced genetic system as to evoke abnormal forms of growth.

Similarly, radiation might evoke leukemia, or in the case of an accumulation of mutations in somatic cells over a lifetime, might alter the metabolic machinery in such a way as to impair its resistance to variations in the external conditions of the environment, and thus trigger a breakdown. Somatic mutation may be involved, but it is not necessary to explain the phenomena.

Mutation as a Random Process

Geneticists have often been quoted as saying that "mutation is a random process," and this has been much misunderstood. It does not mean, of course, that any imaginable sort of effect can be produced by gene mutation within a particular species. The viable modifications are definitely conditioned by the nature of the genes that mutate and by the harmony of the normal processes of metabolism and development. For example, although eye-color mutations in the fruit fly are numerous and of a considerable variety of colors, and although other species of flies have blue or green eyes, yet it seems to be quite beyond the range of possibility for *Drosophila melanogaster* to acquire, by mutation, a blue or green eye color. The spectrum of change is definitely limited. Nor, in the second place, does the randomness of mutation imply that all genes mutate at the same frequency, either spontaneously or when acted upon by ionizing radiations.

Different genes have different stabilities, and under the same conditions some may mutate 100 times as frequently as others. What the "randomness" is intended to imply is that at the present time there is no way of affecting certain genes and not others, at least by means of radiation. All are equally exposed and mutate with a probability in accordance with their individual stability. Two identical genes, one with a recent history of mutation and the other without, will both possess the same mutability. So far, it is impossible to direct the mutation process. Radiation acts blindly, and that is why the deleterious nature of the vast majority of mutations is so important.

By means of several hundred roentgens of radiation, it might indeed be possible to increase the probability of obtaining a desirable mutation in a spermatozoon or egg cell to a chance of one per thousand. At the same time, the probability of getting a lethal mutation would have risen to one in four, and the probability of getting a mutation with some degree of harmfulness would have risen to virtual certainty. That is why we must wait for the slow processes of evolution to sort out the advantageous changes.

Irreversibility and Deleterious Effect of Mutations

Considering the nature of the alterations brought about by radiation in the hereditary material, and, furthermore, the capacity of the latter to replicate itself exactly, we can readily see why the effects of mutation are essentially irreversible. The loss of a part of the genetic material is irreparable, and a large portion of all the hereditary changes induced by radiation consists of such losses. Alterations in the arrangement of the genetic material can be reversed only by an exact rearrangement to the original conditions, which the laws of probability must make exceedingly rare if the chromosomes are broken more or less at random.

Thus, it is not surprising to find that, although spontaneous mutations may undergo reversion to the original state, the radiation-induced ones have rarely, if ever, been observed to do so. Consequently, once a mutation has been produced by radiation and transmitted to the population, it continues its way from generation to generation unless it is either eliminated by the death or failure of its possessor to reproduce, or is excluded by chance from representation in the progeny.

It is also easy to comprehend why the vast majority of mutations have deleterious effects on their possessors. It is now recognized that many, if not all, genes are concerned with the presence and specificity of particular enzymes, each of which governs some one chemical step in the metabolic pattern. There are extremely few biochemical steps in metabolism that can be altered with impunity, and most of them are in fact essential. It is little wonder, therefore, that when a mutation impairs the specificity of an enzyme it blocks a particular metabolic step more or less completely, and the usual outcome is fatal unless the organism has some alternative way of supplying its needs.

These theoretical considerations, which imply that most mutations are expected to be lethal or at least quite detrimental in nature, are supported by the experimental facts. Thus, in *Drosophila* about one-fourth of all mutations are lethal or semilethal, 15 to 20 percent produce sterility in one or both sexes, and nearly all the remainder, whether producing visible morphological changes or not, are subvital (*12*). Less than one in 100 of all mutations—probably nearer one in 1000—is definitely advantageous under existing conditions, although some of the subvital ones might become neutral or even advantageous under altered circumstances.

Most dominant mutations thus quickly lose out in competition with their previously selected, well-adapted alleles which are already established in the species. Only because most mutations are recessive—which is another way of saying that most genes are fairly efficient in a single dose, so that the alteration or

even loss of a single one of the two alleles representing each kind of gene does not block the controlled reaction—is it possible for harmful mutations to accumulate in the gene pool of a population. However, while recessive, harmful mutations do not produce their maximum damage except when inherited in a double dose, through the mating of heterozygous carriers, nonetheless, as studies both of fruit flies and of mice now make clear, the efficiency of the single normal gene is rarely fully equal to that of two. In other words, there is some slight damage from harmful mutations even when they are heterozygous, some loss of fertility, or some impairment of vitality and shortening of the life span, even though no obvious visible defects are to be seen.

This damage, very difficult to measure quantitatively, nevertheless must bear some relation to the load of hidden mutations, which has recently been estimated by Morton, Crow, and Muller (*13*) as amounting to four lethal equivalents per person in the human species. Against the heterozygous damage of harmful genes must be weighed the possibility that mankind, like the fruit fly, is most vigorous in a heterozygous condition—that optimum vigor may result from the balancing of one set of genes that would be harmful if homozygous against another set that would also be harmful if homozygous.

At this point we must confess our present ignorance and await the results of further experiments. Meanwhile, it must be stressed that whereas the just-mentioned benefit of a hybrid nature may apply to man, it is very unlikely that it applies fully all down the viability spectrum, to include the numerous recessive lethal genes as well as the moderately detrimental mutations. Hence it remains imperative to see that the burden of lethals (and seriously crippling defects) in the population does not become too great. It may not matter too much to an individual if he has some new, favorable genes, if at the same time he is hopelessly afflicted. The principle is the familiar one of the acute ailment: one may be in fine shape in every other respect, but a severe toothache or peptic ulcer or migraine sours one's entire outlook on life.

Background Radiation

We come now to appraise the current exposure of the general population to nuclear radiations. According to the views of most geneticists, although not of all, the effects of that exposure can best be weighed in relation to the magnitude of the spontaneous mutation rate, which is currently responsible for a certain amount of tangible genetic defect in the population and for a certain load of wholly or partially hidden mutations carried in individuals who are heterozygous for them. If one could confidently assume that all spontaneous mutation was attributable to the background radiation of the environment, the problem would be fairly simple. Unfortunately, this cannot be done, since the spontaneous mutation rate is in most organisms demonstrably higher than could possibly be caused by the background.

Many years ago Muller and Mott-Smith (*14*) pointed out that for *Drosophila* not more than about 1/1000 of the spontaneous mutation could be caused by the background radiation. For longer-lived animals, a greater fraction may well be caused by the background, since the over-all mutation rate in different species holds fairly constant (within about one order of magnitude), although the exposure to background radiation increases enormously with length of life. If the low-level radiation of the background in fact causes a proportionate amount of mutation, then in a species that lives a thousand times as long as *Drosophila* and whose gonads are equally exposed, all spontaneous mutation would be caused by the background. Haldane (*15*) has argued that this might possibly hold true for man. Man lives about 365 times as long as *Drosophila*, for their reproductive lifetimes are of the order of 30 days and 30 years, respectively. Thus, while it may not be very likely that for man the "doubling dose" of radiation—that is, the dose that would double the total spontaneous mutation frequency—is as small as the amount of the background radiation, it is quite possible that it may be no greater than three times the background.

In the most recent estimate made by the consultants of the National Academy of Sciences Committee on the Genetic Effects of Atomic Radiation, John S. Laughlin and Ira Pullman (*16*), the previous estimate of the background radiation as amounting to a 4.3-roentgen gonadal dose over a 30-year period has been revised downward to 3.1 ± 0.6 rem. Of this amount, cosmic radiation contributes 0.78 ± 0.09 rem; earth and housing 1.59 ± 0.6 rem; atmospheric radioactivity 0.06 ± 0.03 rem; and internal radioactivity (from K^{40}, C^{14}, and radium), beta and gamma, 0.54 ± 0.09 rem, and alpha, 0.15 ± 0.09 rem.

The internal radioactivity of the body is derived mainly from the beta radiation of potassium-40. The data on terrestrial radiation are still meager, but it is evident that there is considerable variation in its amount, depending on whether a person is over sedimentary rock or soil rather than over igneous rock, and on whether the habitation is wooden rather than brick, stone, or concrete. There are also certain areas where a population living on highly radioactive sands is exposed to considerably greater than the usual amounts of radiation—for example, in Brazil and India. On the coast of Travancore, where a fishing population leads a rather primitive life on monazite sands, the 30-year gonadal dose may possibly be as high as 50 or even 150 roentgens (*17*).

If the doubling dose were equal in size to the background radiation, one would expect the frequency of tangible genetic defects in populations living at a particular background level for a sufficient number of generations to approach an equilibrium at a frequency that would vary directly with the amount of the background radiation. If the threefold difference in frequency of congenital defects observed in certain populations compared with others were caused by a threefold difference in the amount of background radiation, it would follow that the doubling dose was equal in magnitude to the background radiation—that is, 3 roentgens. However, it may be argued against this possibility that if the doubling dose were indeed so low, then the frequency of genetic defect in the Travancore population living on highly radioactive soil should approach a frequency of not less than 30 to 40 percent, a level which might have been noticed even though no close study of the situation has yet been made.

Clearly, this is one question for which a genetic analysis is of extreme urgency. If the average gonadal dose of 10 roentgens per person recommended for the general population as a "permissible limit" by the National Academy of Sciences Committee is in fact 3 times the doubling dose, instead of being, as was thought a year ago, probably not above one-fourth of the doubling dose, then a complete reevaluation of the recommendation is called for.

Fallout

No recent revision with regard to the exposure of the general population to fallout from weapons testing has been made, and the figures of a year ago seem to be accurate enough for an evaluation. The extrapolated gonadal dose of 0.1 roentgen per reproductive lifetime at the average rate of fallout over the past 5 years, or of 0.2 roentgen at the maximum rate, amounts to no more than 1 or 2 percent of the recommended maximum allowance and need not cause undue concern. The localization of iodine-131 in the thyroid and of strontium-90 in bone may arouse concern regarding their somatic effects, such as the induction of leukemia, carcinoma, or shortening of

life, but by the same token their localization lessens gonadal exposures from those sources. On the other hand, there is less evidence that cesium-137, another fallout product of importance and long life, is localized within the body and it might even be concentrated to some measure in the reproductive organs. This possibility must be carefully investigated.

Artificial Sources of Radiation

A year ago, in the Report of the National Academy of Sciences Genetics Committee (*18*), the average gonadal exposure of the United States population to medical and dental uses of x-rays, radium, and radioactive isotopes was given a preliminary estimate, based on the studies of our consultants, J. S. Laughlin and I. Pullman, of about 3 roentgens per reproductive lifetime. Their fuller survey of the available data (*19*) revises the probable dose to the gonads upward to 4.6 ± 3 roentgens. Table 1 presents their estimate broken down into categories of dosage.

They have made it clear (as likewise various radiologists have pointed out) that many of the data on which the estimates are based are limited to particular institutions or situations, that there is very great variation in actual practice, and that the statistical uncertainty of the estimates is great. Nevertheless, no better estimates can be made at this time from available data, and they are in agreement with very similar estimates of the exposure of the Swedish population to diagnostic x-rays which are referred to in statements made by the United Nations Scientific Committee on the Effects of Atomic Radiation (*20*). The British estimate of gonadal exposures to diagnostic x-rays is considerably smaller, largely because the average number of examinations per year per person is lower.

In spite of the higher individual exposures of medical personnel and atomic energy employees, occupational exposures add little to the average gonadal exposure of the whole population because of the relatively small number of such persons. It has been estimated, for the United States and Great Britain, respectively, at 3 to 6 percent of the total exposure due to artificial sources. For such individuals and any others subjected to high individual doses, for whatever reason, the problem becomes one of the dosage level at which there will be a significant increase in the probability of tangible genetic damage to their own children and grandchildren. This is why the National Academy of Sciences Genetics Committee has recommended an upper limit of exposure for occupational risk totaling a 50-roentgen gonadal dose from age 20 to age 30 and another 50 roentgens during the succeeding decade of life. The British committee (*21*) made an almost identical recommendation, though in the form of a lifetime total of 200 roentgens and a limit of 50 roentgens from conception to age 30.

Our uncertainty about the precise levels of current exposure to artificial sources of radiation, and the foregoing rough estimates which indicate that the level may well be approaching 50 per cent of the total recommended "permissible dose" for the general population, make it imperative to set up some sort of personal recording of exposures, difficult though that may be from every practical point of view. It is urgently advisable (i) because we so seriously need more precise data about exposures, and record-keeping is one obvious means to this end, even though it may be supplemented and checked by other methods of recording total doses to the population; and (ii) because the existence of such a system of personal records will probably, more than any other factor, provide the atmosphere of caution and prudence so necessary on the part of both the practitioner and the public. In the year since the Genetics Committee's recommendation was made, no definite steps have been taken by public authorities in this direction, so far as I know. Action, at least in the form of pilot efforts, should be specifically urged upon state and federal health authorities at this time.

Competent radiologists have assured members of the Genetics Committee that it should be possible to reduce the average exposure of our United States population by at least half, without diminishing the needed medical and dental diagnostic information. This will be possible not only through the development of new devices, such as faster films and the amplification of fluoroscopic images, so as to provide the same or better information for less exposure, but also by means of more critical attention to proper shielding, filtration, and definition of beam, by reducing the use of fluoroscopy and certain types of pelvimetry which produce heavy exposures (in the latter case of two individuals in the population at once), and by limiting the use of diagnostic x-rays to situations where the information they provide is truly of value. With prudence and the aid of new developments in radiology which are just around the corner, it may even be possible to reduce diagnostic exposures to one-tenth of the current level, at which point they would become a minor problem.

Table 1. Summary of the gentically effective average gonad doses from medical diagnostic x-ray examinations and radiation therapy treatments received per person during one generation (30 years) by the population of the United States (*19*). The minimum average doses have been computed on the basis of the lowest gonadal doses reported. Even further reduction can be obtained since improved techniques are used for some procedures for which the gonad doses are not yet measured. The probable average doses are based on an average of those reported measurements of techniques generally employed.

	Minimum gonad dose (roentgens)	Probable gonad dose (roentgens)
X-ray diagnostic examinations		
Radiography	1.0	1.8
Fluoroscopy	0.3	1.5
Photofluorograms and mass chest x-rays	0.006	0.006
Dental x-rays	0.03	0.1
Obstetrical x-rays	0.16	0.7
Total diagnostic dose	1.5 ± 1*	4.1 ± 3*
X-ray and radioisotope therapy treatments	0.5	0.5
Total gonad dose	2.0	4.6

* Rough limits of error are added in this table on the basis of a verbal communication from J. S. Laughlin and I. Pullman to the Genetics Committee of the National Academy of Sciences. The "total diagnostic dose" is considered by them to be a much firmer estimate than the figure for therapy treatments and, consequently, than the "total gonad dose."

Peaceful Application of Atomic Energy

Finally, it is necessary to look at the situation which is perhaps most likely to create future hazards in this area—namely, the development of atomic energy for peaceful applications. It is stated on good authority that a 100-megawatt heat reactor will produce annually the same quantity of long-lived fission products as the detonation of a 1-megaton fission bomb (*22*). When it is envisioned that by 1965 Great Britain expects to be producing 6000 megawatts of atomic energy, and that within 20 years the United States may produce 20,000 to 40,000 megawatts, it is quite clear that the problem of the safe disposal of these fission products will become one of major proportions.

True, the fission products will normally be contained; but that does not avoid the problem of ultimate disposal. Can we depend on storage underground, with possible contamination of soil and water supplies? The Los Alamos laboratory alone has already used up 40 acres in underground storage and needs a new

site for that purpose. Or can we envision storage in the ocean depths, with the possibility of an overturn of even stable waters sufficient to contaminate marine plant and animal life, and thus eventually all that of the lands adjoining the sea? The very bulk of these long-lived fission products will be so enormous that containment within corrosion-proof vessels, even for 30 to 50 years, will be virtually impossible.

Moreover, the occurrence of accidents, such as an occasional explosion of a reactor or the wreckage in transit of vehicles carrying radioactive materials, cannot be dismissed as too improbable. Atomic power developed on a large scale cannot be immune to accident, any more than any other kind of human enterprise. If even 1 percent of the long-lived fission products produced at a 20,000 megawatt annual level of atomic power were to be released by leakage and accident, the effect would be equivalent to the radiation from 100 bombs of the Hiroshima size.

The threat to mankind of exposure to radiation arising from the peaceful development of atomic energy may thus far outstrip not only that from current exposures due to weapons testing and fallout but even that from the exposures necessary for medical and dental diagnosis. The only immediately obvious escape from so dire an outcome may lie in the rapid development of the hydrogen fusion process as a source of energy.

References

1. H. J. Muller, *Science* 66, 84 (1927).
2. L. J. Stadler, *ibid.* 68, 186 (1928); *Proc. Natl. Acad. Sci. U.S.* 14, 69 (1928).
3. Numerous articles in *A Symposium on the Chemical Basis of Heredity*, W. D. McElroy and B. Glass, Eds. (Johns Hopkins Press, Baltimore, Md., 1957).
4. Compare C. P. Swanson, *Cytology and Cytogenetics* (Prentice-Hall, New York, 1957), chap. 6; H. J. Muller, in *Radiation Biology*, A. Hollaender, Ed. (McGraw-Hill, New York, 1954), vol. I, pp. 351, 475; B. P. Kaufmann, in *Radiation Biology*, vol. I, p. 627; N. H. Giles, Jr., in *Radiation Biology*, vol. I, p. 713.
5. B. Glass, *Brookhaven Symp. Biol.* 8, 148 (1956).
6. D. E. Lea, *Actions of Radiations on Living Cells* (Cambridge Univ. Press, Cambridge, ed. 2, 1955), p. 140 ff.; H. J. Muller, in *Radiation Biology*, A. Hollaender, Ed. (McGraw-Hill, New York, 1954), vol. I, p. 475.
7. W. L. Russell, *Genetics* 41, 658 (1956).
8. A. M. Clark, *Nature* 177, 787 (1956).
9. E. B. Lewis, *Science* 125, 965 (1957).
10. G. Failla, paper presented at AIBS Conference on Basic Problems of Biological Aging, Gatlinburg, Tenn., 2–3 May 1957, unpublished.
11. B. Glass, *Science*, in press.
12. H. J. Muller, *Am. J. Human Genet.* 2, 111 (1950); T. Dobzhansky, *Science* 126, 191 (1957).
13. N. E. Morton, J. F. Crow, H. J. Muller, *Proc. Natl. Acad. Sci. U.S.* 42, 855 (1956).
14. H. J. Muller and L. M. Mott-Smith, *ibid.* 16, 277 (1930).
15. J. B. S. Haldane, *Nature* 176, 115 (1955); F. W. Spiers, *ibid.* 177, 226 (1956); J. B. S. Haldane, *ibid.* 177, 227 (1956).
16. J. S. Laughlin and I. Pullman, unpublished correction to figure cited in *The Biological Effects of Atomic Radiation, Summary Reports* (National Academy of Sciences–National Research Council, Washington, D.C., 1956).
17. A. R. Gopal-Ayengar, "Report of study group on the effect of radiation on human genetics" Copenhagen, August 1956 (World Health Organization, in press); testimony of Shields Warren before Joint Congressional Committee on Atomic Energy, Washington, D.C., 5 June 1957.
18. *The Biological Effects of Atomic Radiation—Summary Reports* (National Academy of Sciences–National Research Council, Washington, D.C., 1956).
19. *The Biological Effects of Atomic Radiation—Gonadal Dose from the Medical Use of X-Rays—Preliminary Report* (National Academy of Sciences–National Research Council, Washington, D.C., 1957).
20. United Nations Scientific Committee on the Effects of Atomic Radiation, *Ann. Internal Med.* 46, 638 (1957); *U.S. Armed Forces Med. J.* 8, 358 (1957).
21. *The Hazards to Man of Nuclear and Allied Radiations* (Medical Research Council—Her Majesty's Stationery Office, London, 1956).
22. E. C. Anderson *et al.*, *Science* 125, 1273 (1957).

W. Bothe, Experimental Nuclear Physicist

Most of today's nuclear physicists are too young to have known the time in which the foundation of their science was laid. The death of Walter Bothe (8 January 1891–8 February 1957) reminds us of the years in which a handful of gifted researchers made one basic discovery after another with very primitive experimental facilities. Their method of working can no longer be imitated today. The field has become too large, the experimental techniques are too involved. However, their way of thinking, the method they employed in choosing, from many possible problems, the important ones, and the way in which they focused their attention on the physical result in spite of great emphasis on experimental technique can be a lesson for us, particularly today when the extension of the experimental method and its problems can all too easily veil the real goal of physical understanding.

Bothe was a student of Max Planck. He therefore started his career as a theoretical physicist. For his Ph.D. thesis he developed the theory of optical refraction and reflection from the scattering of light by single molecules. Max Planck stressed independence in the work of his students. Bothe liked to tell that Planck only twice made a comment on the calculations that were submitted to him. In the first, he said, "This is still insufficient"; in the second, "Now you may finish."

In 1920, after an interruption of nearly 6 years, caused by World War I and long imprisonment in Siberia, Bothe started, with Geiger, his experimental career in physics at the Physikalisch-Technische Bundesanstalt (the German Bureau of Standards). Even from routine measurements in the laboratory he was able to gain new insight which led to publications. However, he soon turned, fully supported by Geiger, to the fascinating problems which the rapidly developing quantum theory set for experimentalists. Geiger's work with alpha rays was carried on in Rutherford's laboratory. Bothe turned his attention to the behavior of beta rays. With the cloud chamber he examined their tracks and, by means of theory, was able to classify the complicated phenomena. His articles on beta rays in the well-known *Handbuch der Physik* are classic examples of the way in which a confused picture may be clarified by theoretical treatment and appear, finally, quite simple.

That was one of the great periods of physics, marked by the penetration of the concept of quanta into "classical" considerations. A large circle of famous physicists was gathered in Berlin, of whom I shall name only Planck, Einstein, v. Laue, and Nernst. The extensive exchange of ideas between them found visible expression in their joint seminars. There, innumerable problems which arose from the new point of view were discussed. Bothe's entrance into this circle resulted in stimulation for experimental investigations, which he then also performed. The best-known result of these endeavors is his work with Geiger, in which it was shown that, in the scattering of light quanta on electrons (Compton-effect), the law of conservation of energy is valid not only on the average but also for the single elemen-

tary process. This was one of the important foundations for the further development in quantum theory.

The investigation on the Compton effect consisted in exploring the simultaneous appearance of scattered light quanta and ejected electrons. The detection of single electrons and x-ray quanta had been made possible a short time earlier with the help of Geiger's point-counter (a forerunner of today's counter tube), which was in such an imperfect form that students, nowadays, would refuse to use it. In each such point-counter the recoil electrons, or the scattered quanta, produced a current impulse; the coincidence of these impulses was determined by registering, on the same moving film, the deflections of two electrometers that were connected to the point-counters. By illumination of both electrometer-threads with the same intermittent light source, the coincidence was established within 1/1000 second.

With this work, a new research tool was established—the coincidence method—which since then has found innumerable applications. At first this new method was developed only as far as was necessary to achieve the physical goal. This is typical of Bothe's working method. The apparatus that he used was thought through completely, but it was built as primitively as possible. He used to say, "a good apparatus has to collapse after the last measurement." Nothing made him as angry as a "work-saving" installation which required more work for its development than it saved. He himself developed the first "coincidence amplifier" as a replacement for the tedious photographic evaluation method and has described its theory completely, but he was openly skeptical about the large expansion in the development of electronic circuits.

The coincidence method soon yielded another fundamental result. Together with Kohlhörster, Bothe succeeded in proving that the mysterious cosmic ultra-radiation consists of very penetrating particles which, in their experiment, made each of two counter tubes, one of which was located above and the other below a large lead block, respond.

This insight, decisive for their field, at once gave the two researchers the idea that, because of the earth's magnetic field, the radiation should be greater at the poles than at the equator. A trip to Spitzbergen failed to confirm this because the increase toward the north is already terminated in our latitudes. However, the travels of other researchers toward the south confirmed the original supposition.

Bothe had turned, in the meantime, to another field in which fundamental findings could still be expected—to the physics of the atomic nuclei. At the start, he used a tool that had not yet been applied in this field, which was then governed by the Rutherford school—namely, the point-counter and the Geiger-Müller counter tube. He was thinking, apparently, of something which, later, he was the first to call "nuclear spectroscopy"—that is, that nuclear transformations are characterized by the type and the energy of the nuclei involved. If nuclei of the same type but of different energies appear, then transitions must be possible which correspond to the emission of light, and this light emission must be coupled in timing with the corresponding particles that arise from transformation. He first investigated, therefore, (with Fränz) the particle energies that appear in certain transformations. He then discovered (with Becker) the gamma radiation that occurs in such transformations. And, thereby, something completely new was discovered. Gamma radiation occurred in the bombardment of elements where previously no particles resulting from transformation had been observed. The quantum energy of the gamma radiation which he was able to determine with a new coincidence method was greater than that of the bombarding particles; it could therefore not be simply a matter of the excitation of an atomic nucleus. To solve this puzzle, several laboratories started to work at once on this problem, until Chadwick solved it with the discovery of the neutron.

Since Bothe was now one of the leading experimental physicists, it was inevitable that the fruitful period of pure research with Geiger should be terminated by calls to universities, which brought him to Giessen and, soon afterwards, to Heidelberg. There he finally took over, again, a pure research institute, the Kaiser-Wilhelm-Institut (now Max Planck Institut), which he directed until his death. With a very small group, the work in nuclear physics was continued. A small Van-de-Graaff generator supplemented the previously exclusive use of radium compounds as sources of radiation. The correlation between particle radiation and quantum radiation in nuclear transformation was proved; in transformations produced by fast neutrons, resonance phenomena were discovered which confirmed Bohr's model of the atomic nucleus, established at the same time. Numerous new transformations could be discovered with hard gamma rays, and it was finally possible also to establish the effect of nuclear isomerism (the appearance of nuclei which differ in energy content only), which had remained a mystery for a long time.

This development was interrupted by World War II and the postwar period. Subsequent years were filled mainly with the training of young physicists, a problem to which Bothe dedicated himself with complete devotion and great success. He died before this activity could bear all its fruit.

In a short, unpublished paper which he wrote a few months ago, Bothe identified himself with a working method with which he himself was able to make exceptional contributions to the progress of physics. He talks of the "intensive working method" as an attempt to recognize fundamental problems and to work them out with a minimum expenditure of money and personnel, in contrast to the "extensive," more diffuse, method, which he admits often reaps the fruits of the primary investigations—something he himself experienced.

Those who knew him know that there was more behind his successes than his working method. Bothe was a man of very extraordinary talents in many spheres outside that of science; he was a deeply artistic man, with a nearly consuming intensity in everything he did as well as in his thinking. Since the sphere of our science has so greatly increased, and since most successes, nowadays, are brought about by the cooperation of many, he will remain, for us, a unique example.

H. Maier-Leibnitz
Laboratory of Technical Physics,
Technical High School,
Munich, Germany

We are indebted to A. M. Akeley of the department of physics, Purdue University, for translating this article from the German.

News of Science

Chicago Low-Temperature Lab

A large noncommercial laboratory for research at temperatures near absolute zero (−460°F) was opened last month at the University of Chicago's Institute for the Study of Metals. The building will be used by physicists, chemists, and metallurgists who since 1945 have been conducting their basic experiments under the west stand of Stagg Field, where the first atomic pile was built and operated in 1942. Earl A. Long, professor of chemistry who has been at the university since 1956 and who was assistant director of Los Alamos Scientific Laboratory during World War II, is director of the Institute for the Study of Metals and of the new laboratory.

The low-temperature laboratory contains equipment that can produce 50 quarts per hour of liquid hydrogen at −423°F, and 8 quarts per hour of liquid helium at −453°F. Additional equipment to permit an output of 20 quarts of liquid helium per hour is planned.

The liquefied gases will be used in the new building's seven experiment rooms. Here, in addition to structural observations, studies will be made of such extreme cold phenomena as superconductivity of supercooled lead and the nature of the liquefied gases themselves—for example, their defiance of gravity and their frictionless flow.

Carnegie Supports Educational Psychology at Northwestern

A 3-year program of teaching, research, and training in educational psychology will be supported at Northwestern University by a grant of $156,000 from the Carnegie Corporation of New York. The Northwestern appropriation is included among new grants totaling almost half a million dollars that have just been announced by Carnegie.

Under the Northwestern program, faculty members of both the school of education and the department of psychology will join together to develop new undergraduate and graduate courses in educational psychology. These courses will include more knowledge of basic research on human behavior than is provided in the usual teacher-training curriculum. The Northwestern group will also outline a program of basic research needed in the field. A portion of the Carnegie funds will be used for the training of graduate students.

Other new Carnegie grants include one of $55,000 to the National Education Association for a conference on gifted students; another of $36,000 to Illinois Institute of Technology for the development of a new approach to mathematics teaching; and one of $66,000 to the University of Maryland for developing an experimental program of mathematics for the junior high school.

Standard Musical Pitch

One of the lesser known services of the National Bureau of Standards is the broadcasting of a musical tone of standard pitch—middle A at 440 cycles per second—over its shortwave stations WWV (Beltsville, Md.) and WWVH (Maui, Hawaii). These broadcasts make standard pitch available day and night throughout the United States and over much of the world. Since a short-wave receiver is all that is needed, easy access to standard pitch is thus provided for piano tuners and amateur and professional musicians as well as for makers of musical instruments.

A 600-cycle-per-second tone is also broadcast. This, together with the 440-cycle-per-second tone, is used by scientists, electronics engineers, and manufacturers in the measurement of short intervals of time and for calibrating instruments and devices that operate in the audio and ultrasonic frequency ranges. Both the 440- and the 600-cycle-per-second tones are obtained from an electronic, crystal-controlled oscillator and are accurate, as transmitted, to better than 1 part in 100 million.

In this country, A = 440 cycles per second has been accepted as standard pitch since 1925. Initially, this value was agreed upon by the Music Industries Chamber of Commerce as a useful compromise among the various pitches chosen arbitrarily by different musical groups. In 1936 the same pitch standard was adopted by the American Standards Association, giving it the status of an industrial standard. Three years later the International Federation of the National Standardizing Associations sponsored a conference in London. France, Germany, Great Britain, Holland, and Italy sent delegates, and the United States and Switzerland sent official messages. Six of the seven countries independently proposed A = 440 as the standard, and the conference adopted it unanimously. The same standard was again endorsed by the International Organization for Standardization in 1953 and was accepted as an ISO Recommendation in 1955.

The National Bureau of Standards maintains the A = 440 standard as the one on which general agreement has been reached. The musical merits of any particular standard are, of course, outside its province.

Previous standards of pitch were defined in terms of the frequency of a particular tuning fork or bar, or the length of a specified vibrating air column (organ pipe). Since the sound frequencies generated by these devices vary with the surrounding temperature, it is necessary to specify the temperature at which comparisons with these standards should be made.

In 1859 the "Diapason Normal" was defined in terms of a standard tuning fork deposited by the French Government at the Paris Conservatory of Music. The vibration frequency of this fork was stated to be 435 cycles per second when measured at the then standard laboratory temperature of 15°C. When R. Koenig (1880) made a careful determination of the frequency, it proved to be 435.45 cycles per second at 15°C and to have a thermal coefficient of −0.0486 cycle per second, per degree centigrade. Thus the fork would really have the defined standard frequency at slightly over 24°C.

From a technical point of view, the present standard of musical pitch, as maintained by NBS, has the advantage that it is free from the vagaries of the material objects (tuning forks, organ pipes) that embodied past standards. A tone is produced that for all practical purposes is independent of the temperature of the surroundings.

U.N. Urges Live Poliovirus Testing

A 12-nation group of experts of the World Health Organization has urged large-scale trials of a new polio vaccine prepared from live virus. The live-virus vaccine is taken by mouth instead of being injected. It is prepared from strains of virus that have been attenuated so that they are no longer able to cause the disease but stimulate protection against it.

If the trials prove successful, accord-

ing to the special WHO committee, the live-virus vaccine will provide reliable and enduring immunity against paralytic poliomyelitis. It would also eliminate or substantially reduce virulent strains. The committee believes that the present Salk killed-virus vaccine is not able to achieve this kind of result. Committee members emphasized that the new vaccine should be considered an adjunct to the Salk vaccine, although it might eventually replace it.

There is an unlikely but possible hazard in the use of the live-virus vaccine, since it has not been conclusively determined whether viruses excreted by immunized persons could prove dangerous to others. Viruses excreted by human beings were injected into the spinal fluid of chimpanzees without harm.

AEC Nuclear Technology Fellowships

Applications are again being accepted for Atomic Energy Commission special fellowships in nuclear technology. These awards are available to students starting their work at the beginning of the second semester or quarter, or third quarter, of the 1957–58 year. The fellowship program is administered for the AEC by Oak Ridge Institute of Nuclear Studies.

Completed applications should be submitted *not later than 15 Oct.* Forms may be obtained from the Fellowship Office, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn.

These fellowships, which carry stipends of $1800 plus tuition and dependency allowances, are open to students with a bachelor's degree in engineering, chemistry, mathematics, or physics, who have completed a course in ordinary differential equations. Fellows must be United States citizens. Before fellowship appointments become effective, the applicant must be accepted as a candidate for a graduate degree by an institution participating in the program. A list of these institutions is included with the application form, and applicants may make their choice from among them.

Proposed Legislation

Of the many bills introduced in Congress, some have a special relevance to science and education. A list of such bills introduced recently follows:

S 2447. Authorize and direct Secretary of Interior to undertake continuing studies of effects of insecticides, herbicides, and fungicides upon fish and wildlife for purpose of preventing losses of those natural resources following spraying and to provide basic data on various chemical controls so that forests, croplands, and marshes can be sprayed with minimum losses of fish and wildlife. Magnuson (D Wash.) Senate Interstate and Foreign Commerce.

HR 8461. Amend Atomic Energy Act of 1954 to provide for appointment of representatives of U.S. in organs of International Atomic Energy Agency; make provisions re participation of U.S. in that agency. Cole (R N.Y.) Joint Atomic Energy.

S 2490. Provide for control of noxious weeds on land under control or jurisdiction of Federal Government. Humphrey (D Minn.) Senate Agriculture and Forestry.

HR 8571. Provide federal insurance for loans made to science and engineering students. Lane (D Mass.) House Education and Labor.

HR 8629. Protect public health by amending the Federal Food, Drug, and Cosmetic Act to prohibit the use in food of additives which have not been adequately tested to establish their safety. Wolverton (R N.J.) House Interstate and Foreign Commerce.

H J Res 399. Amend act of Congress approved 7 Aug. 1935 (PL 253), concerning United States contributions to the International Council of Scientific Unions and certain associated unions. O'Hara (D Ill.) House Foreign Affairs.

S 2501. Authorize 88 positions for specially qualified scientific and professional personnel in the Department of Commerce at rates of compensation not to exceed the maximum rate payable under PL 313, 80th Congress, as amended, and PL 854, 84th Congress. Johnston (D S.C.) Senate Post Office and Civil Service.

News Briefs

Columbia University has received a large collection of documents by and about the late Otto Rank, psychotherapist and student and associate of the late Sigmund Freud. Also included among the gifts were three of Freud's original manuscripts.

* * *

The French research reactor at Saclay has begun to operate on nuclear energy, utilizing heavy water made available to France by the U.S. Atomic Energy Commission.

* * *

The Philadelphia College of Osteopathy has announced plans to erect an osteopathic center on a 16-acre tract in Philadelphia at a cost of $10 million. Among the buildings will be two hospitals, with a total of 600 beds.

* * *

National Science Foundation publications are available to all scientists who have need for them. Lists of publications may be obtained from the foundation. Requests should be addressed to the Publications Office, National Science Foundation, Washington 25, D.C.

* * *

The corporate name of North American Instruments, Inc., has been changed to Northam Electronics, Inc. The company is a subsidiary of Norris-Thermador Corporation, with headquarters in Los Angeles, Calif.

* * *

A centennial program in memory of Elisha Mitchell, chemist, geologist, and mathematician, was held on the summit of the mountain near Asheville, N.C., that bears his name. It was the second of three programs planned by the University of North Carolina in observance of the centennial of Dr. Mitchell's death. The third will take place this fall at Chapel Hill.

* * *

The blue whale, the biggest animal ever known to exist, is in danger of becoming extinct owing to overhunting. Under international treaty, each year's take is limited, but it is feared that, unless the killings are further reduced, the species may not survive.

* * *

Aerojet-General Corporation, Azusa, Calif., has announced the establishment of a new Astronautics Research Laboratory for investigation in propulsion, astrophysical chemistry, and materials.

* * *

A lifelike cast of *Latimeria*, the living coelacanth and survivor of a 300-million-year-old species, is being exhibited at the American Museum of Natural History, New York. It was purchased from the Natural History Museum in Paris.

* * *

BJ Electronics, a facility of Borg-Warner Corporation, has begun operation of a new electronic performance and environmental testing laboratory at Santa Ana, Calif.

* * *

Total iron-ore resources of the United States are about 75 billion long tons of crude ore, according to a recent estimate by the U.S. Geological Survey. Since the last summary of iron-ore resources was published in 1955, the estimated total of major deposits has been increased by more than 25 billion long tons, partly as the result of further exploration and more complete information but principally by the inclusion of additional low-grade material in the Lake Superior region.

Career Choice of Merit Scholars

The 1957 Merit Scholarship Program conducted a survey of the career choices and proposed fields of specialization in

college of the Merit Scholars and finalists. Results of the survey for scholars and for students who became finalists in the competition are listed in Table 1.

Table 1. 1957 Merit scholarship program.

Career	Scholars		Finalists	
	Boys	Girls	Boys	Girls
Career choice				
Engineering	158	5	1657	54
Research				
Academic	19	7	166	63
Industrial	170	44	1170	314
Government	7	2	77	22
Medicine				
Physician	46	23	414	124
Related fields (nursing, technology, pharmacy)	2	4	35	130
Teaching	74	74	392	771
Business	40	12	257	97
Law	36	3	318	22
Ministry	14		96	7
Government service	10	8	105	119
Social work, psychology	6	7	46	105
Library work		3	1	16
Writing, journalism, radio	11	11	103	172
Arts: design, music, theater	4	5	79	79
Agriculture, forestry	2		15	1
Miscellaneous	1	1	6	22
Undecided or no information	14	8	290	151
Total	614	217	5227	2269
Proposed fields of specialization in college				
Engineering				
Aeronautical	11		151	4
Chemical	40	2	358	17
Civil	8		114	2
Electrical	51	1	526	7
Mechanical	17		245	4
Metallurgical, mining	5		23	1
Architecture	3		44	7
Not specified	26	1	272	9
Total	161	4	1733	51
Science				
Biology	12	5	80	86
Premedical	29	16	299	100
Chemistry	45	35	414	220
Geology, geophysics	8	1	34	4
Mathematics	49	27	304	216
Physics	122	13	833	71
Not specified	14	7	93	178
Total	279	104	2057	875
Liberal arts				
Humanities	46	53	360	599
Social sciences	74	35	541	455
Not specified	8	4	72	26
Total	128	92	973	1080
Business	26	4	151	41
Miscellaneous	10	11	86	162
Undecided or no information	10	2	227	60
Total	614	217	5227	2269

Scientists in the News

PAUL E. KLOPSTEG has been named associate director for research of the National Science Foundation. Formerly an associate director of the foundation and more recently an NSF consultant, he will now be responsible for the foundation's activities in support of basic research in the sciences. Klopsteg has been professor of applied science and director of research at Northwestern Technological Institute, Evanston, Ill., and is professor emeritus at Northwestern University.

A. M. PAPPENHEIMER, JR., chairman of the microbiology department in the College of Medicine, New York University, will become professor of biology at Harvard University a year from now. He will direct the program of tutoring in the biochemical sciences in Harvard College. This includes some 150 undergraduates preparing for careers in medicine and biological research.

While he was senior chemist at the Massachusetts State Antitoxin and Vaccine Laboratory before World War II, Pappenheimer isolated the diphtheria toxin in purified form. He has since studied toxin production by the diphtheria bacillus and the mechanism by which toxin exerts its lethal action. His recent research has centered on delayed hypersensitivity, especially the allergy resulting from chronic bacterial infections.

SHERWOOD K. HAYNES, professor of physics at Vanderbilt University, has been named head of the department of physics and astronomy at Michigan State University. He will take up his new duties on a part-time basis on 1 Sept. and full time next 1 Feb.

J. B. S. HALDANE, professor of biometry at University College, London, and one of Britain's leading geneticists, left England on 24 July to settle in India. He was accompanied by his wife, Helen Spurway, who has been a lecturer on genetics and animal behavior at University College. The two scientists will work together in the Indian Statistical Office in Calcutta.

CHARLES S. HOWARD retired 31 July after 37 years as chemist with the water quality branch, Water Resources Division, U.S. Geological Survey. With W. D. Collins, former chief of the branch, he did pioneer work in investigations of water quality throughout the United States.

Howard joined the survey in 1920 after a year as chemistry teacher at the U.S. Naval Academy. He has written many papers on the chemistry of water and is particularly well known for his contribution to knowledge of the sediment and chemical characteristics of the Colorado River. He earned his B.S. degree at Worcester Polytechnic Institute in 1918, his M.S. degree at American University in 1925, and his Ph.D. degree at American University in 1928.

JOHN B. BROWN, specialist in the chemistry of fats, has been appointed chairman of the department of physiological chemistry and pharmacology at Ohio State University, succeeding CLAYTON S. SMITH, who retired from active teaching duties this summer after 37 years of service. The new chairman, a member of the Ohio State faculty since 1924, continues also as director of the university's Institute of Nutrition and Food Technology.

MICHAEL T. CRONIN has been named manager of the newly formed department of toxicology and pathology in the research laboratories of Schering Corporation, Bloomfield, N.J. He previously had been associate pathologist at Penrose Research Laboratories, Philadelphia, Pa., and assistant professor of veterinary pathology at the University of Pennsylvania.

MICHAEL HEIDELBERGER started on 1 Aug. upon a deferred terminal sabbatical leave from Columbia University, where he is now emeritus professor of immunochemistry. He will present a paper at the second International European Congress on Clinical Chemistry in Stockholm (19–23 Aug.) and then visit a number of European countries. From October until January, on leave from Rutgers University, he will conduct research and lecture at the Faculté de Pharmacie of the University of Paris. In about the middle of January 1958 he is to give the York lecture at the University of British Columbia, Vancouver, after which he will return to Rutgers University to resume his duties as visiting professor of immunochemistry.

The New England Center Hospital has announced the establishment of a new department of infectious diseases under the direction of LOUIS WEINSTEIN who, in addition to being named chief of the new unit and senior physician at the hospital, has also been appointed professor of medicine at Tufts University School of Medicine. Both the hospital and the medical school are part of Boston's New England Medical Center. To accept these appointments, Weinstein has resigned as chief of the Infectious Diseases Service at Haynes Memorial of the Massachusetts Memorial Hospitals and as associate professor of medicine at Boston University School of Medicine.

MAX W. GARDNER, for 25 years professor of plant pathology at the University of California, became professor emeritus on 1 July. He was chairman of the Berkeley-Davis departments of plant pathology from 1936 to 1954. He plans to continue residence in Berkeley.

WILLIAM C. STADIE, professor emeritus of research medicine, University of Pennsylvania, has received the Alvarenga prize of the College of Physicians of Philadelphia for his contributions to knowledge of carbohydrate metabolism. The Alvarenga prize was established by the will of Pedro Francisco DaCosta Alvarenga of Lisbon, Portugal, as associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the college on the anniversary of the death of the testator, 14 July 1883.

WALTER L. MALLMANN, professor of microbiology and public health at Michigan State University, will make a study in the eastern Mediterranean countries for the World Health Organization. Mallmann, who has written more than 200 books and articles on various phases of bacteriology, will survey the food in the countries from a public-health aspect.

Besides his 3-month study for WHO, Mallmann will also visit various laboratories in Europe. He will be on leave from Michigan State from 1 Sept. 1957 to 31 May 1958.

ALFRED L. COPLEY, formerly of New York City, has accepted a position as director of experimental research in vascular diseases at the new Medical Research Laboratories, Charing Cross Hospital, part of the University of London. Copley, an experimental physiologist, has been working since 1952 in Paris, France, at first as head of the Laboratory of Physiology at the International Children's Center, and later as Chargé de Recherches of the Institut National d'Hygiène. Copley's work will, as in Paris, also be aided by a grant from the National Science Foundation, Washington. He will continue his investigations of the endothelium in relation to hemorrhage and of thrombosis and atherosclerosis.

JOHN H. CONOVER has been named meteorologist and acting director of the Harvard University's Blue Hill Meteorological Observatory, effective 1 Sept. He will be in charge of the observatory in the interim between the retirement this summer of CHARLES F. BROOKS, professor of meteorology at Harvard and long-time head of the university's weather research station, and the arrival of RICHARD M. GOODY, British physicist, who will become professor of meteorology and observatory director on 1 July 1958.

ERICH FROMM, director of the department of psychoanalysis at the National University of Mexico, has joined the staff of Michigan State University as professor of psychology. He will conduct a concentrated seminar, the first half to be given in October and the other half in the spring term. He will also be available for consultation with the faculty and graduate students in the social sciences and related fields. Fromm, author of *Escape from Freedom* and the recently published *The Art of Loving*, will continue to spend a major portion of his time on research in Mexico, where he currently is investigating factors influencing the social and psychological revitalizing of a Mexican village.

SPAS S. IVANOFF, acting head of the department of plant pathology and physiology at Mississippi Agricultural Experiment Station, has been named head of the department.

WILLIAM V. MAYER, acting head of the department of biology at the University of Southern California, Los Angeles, has been appointed chairman of the department of biology at Wayne State University, effective 1 Sept. 1957.

ALLEN H. SCHOOLEY has resumed his position as superintendent of the Electronics Division at the Naval Research Laboratory in Washington, D.C., after a year's leave of absence as an adviser to the Brazilian Navy in matters related to the establishment of a Brazilian Naval Research Institute.

GEORGE GAMOW, professor of physics at the University of Colorado, will give the sixth annual Edsel B. Ford lecture on 8 Oct. in the auditorium of the Henry Ford Hospital in Detroit, Mich. He will discuss "Molecular genetics." The lecture will be given under the combined auspices of the Henry Ford Hospital Medical Society and the Edsel B. Ford Institute for Medical Research.

ROLAND W. WINTERFIELD, formerly research professor in the department of veterinary science at the University of Massachusetts, has joined the staff of the American Scientific Laboratories, Inc., Madison, Wis., where he is associate research veterinarian. He is a specialist in poultry respiratory diseases.

This year's honorary degree recipients include the following:

CHARLES B. HUGGINS, professor of urology and director of the Ben May Laboratory for Cancer Research at the University of Chicago, from Torino University, Italy.

JOSEPH KAPLAN, professor of physics at the University of California, from Carleton College and from Notre Dame University.

E. W. R. STEACIE, president of the National Research Council of Canada, from St. Lawrence University.

HAROLD B. TUKEY, head of Michigan State University's department of horticulture, from Hannover Institute of Technology, Germany.

Recent Deaths

ERNST A. BESSEY, East Lansing, Mich.; 80; emeritus professor of botany at Michigan State University, early in his career professor of botany at Louisiana State University; secretary of AAAS Section G, Botanical Sciences, in 1901; 17 July.

ROBERT CHAMBERS, Concord, N.H.; 75; until recently chief of the Laboratory of Experimental Cell Research, Marine Biological Laboratory, from 1928 to 1947 research professor of biology at Washington Square College, New York University, and previously professor of microscopic anatomy at Cornell Medical College; past president of the Union of American Biological Sciences, the American Society of Zoologists, and the Harvey Society; 22 July.

ALFRED E. COHN, New Milford, Conn.; 78; specialist in the human heart and emeritus member of Rockefeller Institute for Medical Research; made fundamental contributions to the technique of electrocardiography and was the first to use the electrocardiograph in the U.S.; author of philosophic and humanistic, as well as scientific, works; 20 July.

JAMES L. FINCH, Mineola, N.Y.; 64; assistant chief engineer for Radio Corporation of America Communications, inventor and pioneer in international radio communication; 22 July.

JOSEPH B. HERSHMAN; 57; former president of Valparaiso Technical Institute, director of radio, Dodge's Telegraph and Radio Institute; 29 June.

WELLINGTON D. JONES, St. Joseph, Mich.; 71; emeritus professor of geography at the University of Chicago, for a period dean of science in the College of Arts, Literature and Science, and in 1924–25 associate dean of the College; 24 July.

C. S. McDOWELL, Bohemian Grove, Calif.; 72; engineer, formerly president and general manager of Arma Corporation, supplier of naval apparatus, coordinating engineer for the building of the Mount Palomar telescope; helped to found the New London, Conn., submarine school; 18 July.

JOSEPH R. MINEVITCH, Boston, Mass.; 65; chemical engineer and president of the newly formed J. R. Minevitch and Associates; plant designer; 3 July.

Reports

Nature of Solvent Transfer in Osmosis

The phenomenon of osmosis appears to be looked upon with sharply differing points of view by many physiologists and others in related disciplines. The traditional view of workers in the field of capillary and glomerular permeability, as typified by the work of Starling and Landis and, in more recent years, by the work of Krogh, Ussing, and Jacobs holds that osmosis is a *mass* flow of the solvent through the "pores" of the barrier (membrane) arising by some obscure mechanism—usually not discussed—when a mole fraction difference of the solvent obtains by virtue of the presence of a macromolecule impermeable to the barrier. Another point of view has argued exclusively for the *diffusion* of the solvent—that is, a molecular-molecular random drift. This view has been most eloquently expressed in recent years by Chinard (*1*).

Although several workers (*2*) in recent years have demonstrated that osmotic transfer must be viewed as a mass flow, this work has been carried out on biological material and for this reason might appear to be ambiguous or inconclusive since more "complex" phenomena might be involved. The data presented in this report (*3*) have been obtained on a simple system to help focus attention on the fundamental process of osmotic transfer. It will be seen in the following discussion that two irreversible processes can take place, and usually do, to a varying degree. A simple binary system—namely, a solvent (water) and an uncharged macromolecule—is considered in conjunction with a typically inert barrier as used in osmometry of the Fuoss-Mead type (perforated stainless-steel disk covered with collodion) to which the macromolecule is *absolutely* impermeable.

The first task is to establish the nature of the solvent flux when a hydrostatic pressure difference is applied across the barrier. Direct observation on this barrier indicates a linear relationship between hydrostatic pressure and transfer of solvent, namely, 0.88×10^{-10} mole/sec, per dy/cm^2.

The diffusion component of flux can be evaluated by applying the general relationship (4)

$$\frac{dn}{dt} = -\frac{DA}{RT} C \frac{\Delta\mu}{\Delta X} \qquad (1)$$

where A is the effective area and D the self-diffusion coefficient of the solvent and μ is the chemical potential. This equation can be rewritten

$$\frac{dn}{dt} = -\frac{DA}{RT} \frac{\Delta P}{\Delta X} \qquad (2)$$

since

$$\Delta\mu = \overline{V}\Delta P$$

and

$$C\overline{V} = 1$$

The factor $DA/\Delta X$ can be evaluated, after observing the diffusion of H_2O^{18} across the same barrier, from the relation

$$\left(\frac{dn}{dt}\right)_{H_2O^{18}} = DA \frac{\Delta C_{H_2O^{18}}}{\Delta X} \qquad (3)$$

Integration of this, with the assumption of a linear gradient, yields the equation

$$\frac{DA}{\Delta X} = \frac{2.3V}{2\Delta t} \log \frac{C' + C'' - 2C''_t}{C' + C'' - 2C''_{t+\Delta t}} \qquad (4)$$

in which C′ and C″ (C′ > C″) are the initial concentrations of H_2O^{18}. A cell was constructed with equal volumes ($V = 6.5$ cm^3), and means for stirring were provided. Samples were taken at intervals of time Δt (15 min), with the first sample taken at time t several minutes after the cell had been filled. Analyses were made with a mass spectrometer. Typical data obtained for the initial concentrations $C' = 1.3$ percent and $C'' = 0.2$ percent are $C''_t = 0.28$ percent, $C''_{t+15} = 0.54$ percent, and $C''_{t+30} = 0.65$ percent. With these data, Eq. 4 gives $DA/\Delta X$ as 3×10^{-3}. Thus, by means of Eq. 2, the magnitude of flux per unit pressure difference is 0.12×10^{-12} mole/sec, per dy/cm^2. Comparison of this with the magnitude found experimentally shows that the diffusion component is about 1/730 of the total flux.

One is forced to conclude, therefore, that any pressure difference applied gives rise to a transfer of water which is predominantly nondiffusional in nature. It will be convenient to refer to this component as quasi-laminar since the flow lines in the barrier would be difficult to establish.

The osmometer experiment is now to be considered. It is an experimental fact that the transfer of water through the barrier when a hydrostatic pressure difference is applied can be duplicated in the *absence* of a pressure difference by contaminating one volume of the solvent with a macromolecule—for example, dextran—to which the barrier is *absolutely impermeable*. The quantity, which is exactly equivalent to a given value of ΔP, is $(RT/\overline{V})$ in N_{H_2O} which reduces to RTc for small values of the concentration c of the macromolecule.

The fascinating nature of the mole fraction effect can be seen in that, while "intuitively" one might assume that this component of the chemical potential would give rise to a diffusion flux as prescribed by Eq. 1, the experimental fact observed is that the flux developed is predominantly nondiffusional but, as termed in a preceding paragraph, "quasi-laminar." This conclusion is inescapable since, in the osmometer experiment, we observed the equivalence of the mole fraction and the hydrostatic pressure variables and in the first experiment we established the nondiffusional nature of the flux due to hydrostatic pressure. Therefore, the mole fraction effect must also develop a nondiffusional flux. Thus, expressing this symmetrical relationship, we have

$$\frac{dn}{dt} = K f(A) [\Delta P - \pi]$$

where positive value of flux is defined from solution to solvent and ΔP is the excess hydrostatic pressure on solution over that of solvent, and π is the mole fraction term. The proportionality constant is some kind of "hydraulic conductivity" depending upon the nature of the flow process.

It should be emphasized that there is no kinetic theory in existence to explain the basis of the nondiffusional flux arising from the mole fraction effect. Unfortunately, the theory of liquids is inadequate at the present time for carry-

All technical papers and comments on them are published in this section. Manuscripts should be typed double-spaced and be submitted in duplicate. In length, they should be limited to the equivalent of 1200 words; this includes the space occupied by illustrative or tabular material, references and notes, and the author(s)' name(s) and affiliation(s). Illustrative material should be limited to one table *or* one figure. All explanatory notes, including acknowledgments and authorization for publication, and literature references are to be numbered consecutively, keyed into the text proper, and placed at the end of the article under the heading "References and Notes." For fuller details see "Suggestions to Contributors" in Science 125, 16 (4 Jan. 1957).

ing out more than speculative analysis, but certainly, as suggested by Lars Onsager, there must be a momentum deficiency in the microdomain of the pore in the solution side of the barrier. That is, in a solid region of the barrier, the time average transfer of momentum is that prescribed by the hydrostatic pressure of the phase, but in the opening of the pore there is a deficiency since the momentum arising from the macromolecule is not transferred to the solvent species in the pore, being cut off by the finite size of the pore. Thus, within the pore and only within the pore, a gradient of pressure arises and quasi-laminar flow ensues from the solvent side to the solution.

Although the experimental observations in the osmometer experiment do not demonstrate the diffusion component of flux explicitly, it is reasonable to assume that this component is present:

$$\left(\frac{dn}{dt}\right)_{diff.} = \frac{-DA}{RT} C \frac{\Delta\mu}{\Delta X} \cdot$$

$$= \frac{DA}{RT} \frac{C}{\Delta X} [\overline{V}\Delta P + \Delta RT \ln N]$$

$$= \frac{DA}{RT} \frac{C\overline{V}}{\Delta X} [\Delta P + \frac{RT}{\overline{V}} \ln (1 - N_{H_2O})]$$

$$= \frac{DA}{RT} \frac{1}{\Delta X} [\Delta P - \pi]$$

Thus, the total flux is

$$\frac{dn}{dt} = \left[\frac{DA}{RT\Delta X} + K f(A)\right] [\Delta P - \pi]$$

The diffusion component would be all-important in a barrier whose "pores" have a cross-sectional area of the order of the solvent molecules such that only a molecular-molecular drift of the solvent could occur.

In conclusion, the point to be emphasized for workers in the field of membrane permeability is the fact that in osmotic transfer the chemical potential difference of the solvent can give rise to both a quasi-laminar flux and to a diffusion flux, the relative importance of the two components being dependent on the nature of the barrier. For most barriers, the predominant component is the quasi-laminar flux.

ALEXANDER MAURO
Department of Physiology,
Yale University School of Medicine,
New Haven, Connecticut

References and Notes

1. F. P. Chinard, *Am. J. Physiol.* 171, 578 (1952).
2. V. Koefoed-Johnson and H. H. Ussing, *Acta Physiol. Scand.* 28, 60 (1953); E. Zeuthen and D. M. Prescott, *ibid.* 28, 77 (1953); R. P. Durbin, H. Frank, A. K. Solomon, *J. Gen. Physiol.* 39, 535 (1956).
3. I am deeply indebted to my colleagues H. Morowitz, J. H. Wang, D. Hitchcock, G. Meschia, and Lars Onsager for their kind help with theoretical discussions and experimental details.
4. G. S. Hartley, *Phil. Mag.* 12, 473 (1931).

3 May 1957

Aggressive Behavior in Castrated Starlings

Androgens have long been known to affect the aggressive behavior of birds and mammals. Experiments conducted during the last two decades have shown that animals of various species ceased aggressive behavior when they were castrated, or rose in social rank when they were given injections of testosterone. This paper (*1*) reports the maintenance of aggressive behavior in castrated starlings and the failure of testosterone to affect their social rank.

The methods consisted of observing castrated starlings (*Sturnus vulgaris*) that were living in a large room (14 by 16 feet). Eleven birds were bilaterally castrated on 20 Dec. 1956, when the testes were still in the regressed winter condition but were starting to increase. The birds were painted on the tail with bright colors for individual identification. These birds maintained fighting and singing behavior for a month. A conventional diagram describing the social rank was prepared. In most cases the relative position was clear, but in some cases the birds may have been tied for position, and in other cases no contests were observed.

On 15 Jan. a series of injections of graded doses of testosterone was begun, to determine the effect of testosterone on the seminal vesicle (*2*). The dosage was not known to the observer. The rank of the individuals did not change during a period of 10 days. The birds that were injected with control material remained in their rank. The birds that received the highest amounts of testosterone were sixth and ninth in rank even at the end of the 10-day period. It was suspected that three of the birds might have some testicular tissue because their bills remained yellow. These birds ranked first, third, and eighth and, on autopsy, were found to have some tissue.

Because these results were the gleanings from another experiment, a program was specifically planned. Five birds were castrated 2 Feb. and were observed until 11 Mar. A rank was obvious, and song continued vigorously. Injections of testosterone (begun 11 Mar.) at various dosages had no effect on rank. On autopsy, on 21 Mar., one bird (second in rank) had 25 mg of testicular issue, but the top-ranking bird had none.

These results demonstrate that castrated male starlings maintain a rank, as do normal birds. Since the aggressiveness of these adults might be the result of learning, experiments with young birds are planned. However, the aggressiveness might result from androgen from another source. But the threshold of response would have to be below the level that controls bill color and growth of seminal vesicles because castrated birds have black bills and minute seminal vesicles. Furthermore, the fact that injections of large amounts of testosterone did not alter rank indicates that androgens are not involved. The aggressiveness might be responsive to another hormone, such as a hypophyseal hormone, since Witschi (*2*) concluded that, in some birds, plumage changes are controlled by gonadotropins. This possibility is being explored.

DAVID E. DAVIS
Division of Vertebrate Ecology,
Johns Hopkins School of Hygiene
and Public Health, Baltimore Maryland

References and Notes

1. This work was conducted under a grant from the National Institute of Mental Health.
2. A description of this work is in preparation.
3. E. Witschi, *Mem. Soc. Endocrinol.* 49, 149 (1955).

25 April 1957

Nature of Fluorophore Localizing in Tetracycline-Treated Mouse Tumor

It has been previously observed that certain chemical agents such as fluorescein (*1*) and hematoporphyrin (*2*), when administered parenterally to tumor-bearing animals, tend to localize in the tumor tissue. This phenomenon finds limited clinical applications in the localization and diagnosis of neoplastic diseases (*3*). The fluorophore in the tumor tissue was usually assumed to be the unchanged compound administered, without, however, inquiry being made into its exact chemical nature.

Recently, Rall *et al.* (*4*) reported that, in animals bearing transplantable tumors, localized fluorescence was noted in the bones and the tumor tissue after treatment with any of the tetracyclines. The discovery aroused considerable interest in that a variety of animal tumors as well as a few human neoplasms exhibited this behavior. In addition, the localized fluorescence persisted as long as the animals survived (*5*).

In view of the sustained interest in the problem and the obvious chemotherapeutic possibilities implied, an effort has been made in our laboratory to study the chemistry of the fluorophore in the tetracycline-treated mouse tumor. In this report, evidence is presented to show that the localized fluorescence is attributable to unchanged tetracycline which, however, probably does not exist as such in the tumor tissue, but rather as a loose complex bound with a peptide which is one of the normal constituents of mouse sarcoma tissue.

CAF_1 mice weighing 20 to 24 g with 6-day-old sarcoma S-37 were injected in-

traperitoneally with tetracycline hydrochloride (*6*) (3 mg in 0.3 ml of saline). Following three such daily treatments, the mice were sacrificed on the third day after the last injection, and, under ultraviolet illumination (*7*), the fluorescent parts of the tumor were excised. The tumor tissues collected were homogenized in water, about 2 ml/g of tissue, and the homogenate was dialyzed in cellulose casing (*8*) with shaking against dilute hydrochloric acid (0.1*N*, about 8 ml for every gram of tissue) for 2 hours (*9*). The dehydration of tetracycline to anhydrotetracycline (*10*) is very fast in acid stronger than 0.1*N*; nevertheless, in 0.1*N* hydrochloric acid, tetracycline is stable for at least 4 hours. When the *p*H of the filtered dialyzate was adjusted to above 7 by the addition of sodium hydroxide, the fluorophore inevitably came down as a flocculent precipitate which fluoresced bright greenish yellow under ultraviolet light. Under identical experimental conditions, from the dialyzate of the tumor tissue of control mice that received no tetracycline, there was likewise obtained a flocculent precipitate which was, however, nonfluorescent. In both cases, the precipitates gave positive ninhydrin and biuret tests, thus suggesting their peptide nature. For the electrophoresis and paper chromatography experiments described in the following paragraphs, a more concentrated solution of the fluorophore (and similarly of the peptide in untreated mouse tumor) could be conveniently prepared by first separating the precipitate by centrifugation, then washing with a little water, following with centrifugation again, and finally dissolving in a minimum amount of 0.1*N* hydrochloric acid.

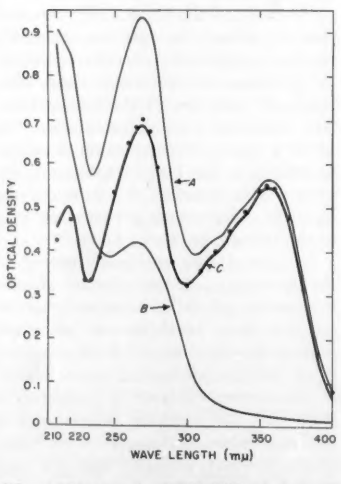


Fig. 1. Spectra in 0.1*N* HCl of (*A*) the fluorophore, (*B*) the nonfluorescent precipitate from control tumor, and (*C*) tetracycline (18 μg/ml). The closed circles are the calculated optical densities due to the prosthetic group of the fluorophore.

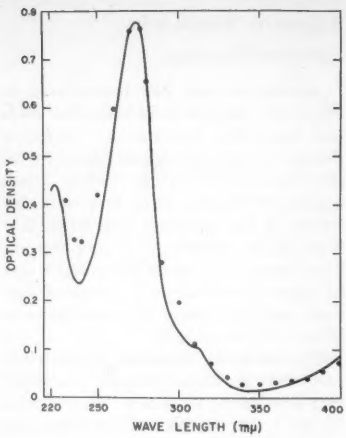


Fig. 2. Spectrum of anhydrotetracycline (6.7 μg/ml in 1*N* HCl). The closed circles denote the calculated optical densities due to the altered prosthetic group of the tetracycline.

At *p*H higher than 7, after saturation of the alkaline dialyzate with salt, the fluorophore could be partially extracted into butanol. Examination of the ultraviolet absorption spectrum of the butanol extract against a similar extract of the control tumor tissue as blank revealed that, compared with the spectrum of tetracycline itself in butanol, the $\lambda_{max.}$ at 367 mμ of the parent compound had undergone a shift of 15 mμ to 382 mμ (*11*, *12*). Such a bathochromic shift—analogous to, for example, that observed of chlorophyll in plant cells (*13*)—could be ascribed to the formation of a complex between tetracycline and the peptide in tumor tissue. This view receives further support from the results of paper-electrophoresis and paper-chromatography experiments. In the former experiments, using the Spinco model R electrophoresis cell of the Durrum type, at a constant voltage of 250 in *p*H 8.6 barbiturate buffer, the migration rate of the fluorophore differed quite noticeably from that of tetracycline. As for the paper-chromatography work, the sodium arsenite system, with ascending flow (*14*), was employed. The R_f value for the fluorophore was observed to be about 0.10 as against 0.16 for tetracycline.

However, in weak acid—for example, 0.1*N* hydrochloric acid, a comparison of the ultraviolet spectrum of the fluorophore with that of tetracycline and also of the nonfluorescent precipitate from control mouse tumor displayed no new absorption bands, nor did it display any shift of the existing bands (Fig. 1). It seems safe, therefore, to conclude that the complex formed between tetracycline and the peptide must be a loose one; in fact, the complex readily dissociates in acid. Assuming that the peptide of the control and that of the tetracycline-treated tumor exhibit identical ultraviolet-absorption patterns, it is easy to calculate the absorbance owing to the prosthetic group of the fluorophore at various wavelengths by simply deducting the corresponding absorbance owing to the peptide from the total absorbance. The reasonableness of the assumption at once becomes evident; through the outcome of the calculations, an absorption curve of the prosthetic group can be constructed, which is exactly identical with the spectrum of tetracycline at 18 μg/ml in 0.1*N* hydrochloric acid (Fig. 1).

The identification of the prosthetic group of the fluorophore with tetracycline is further strengthened by the observation that, as a result of the exposure to 1*N* hydrochloric acid for 1 hour or longer, the fluorophore disclosed profound changes in its ultraviolet absorption spectrum. By applying the same mathematical technique, we calculated the absorbance contributed by the altered prosthetic group and plotted it against the wavelength (Fig. 2). For all practical purposes, the absorption curve represents nothing but the spectrum of anhydrotetracycline. This is hardly surprising, for it is known that the conversion of tetracycline into the anhydro-compound proceeds with rapidity in acid.

Thus, without actually isolating the prosthetic group, it has been possible to demonstrate that the fluorophore in the tetracycline-treated mouse tumor is most likely a complex formed of the parent compound and a peptide. This complex dissociates readily into its components in acidic media. At present, the mechanism for the localization and persistence of the tetracyclines in the tumor tissue remains unclear. Work is currently in progress in our laboratory on the metabolism of the tetracyclines and also on other compounds closely related to the tetracyclines that might manifest this phenomenon. The chemistry of the peptide associated with tetracycline is being actively investigated (*15*).

Ti Li Loo
E. D. Titus
D. P. Rall

National Cancer Institute,
National Institutes of Health,
Bethesda, Maryland

References and Notes

1. F. H. J. Figge, *Cancer Research* **2**, 335 (1942); also later papers.
2. G. E. Moore, *Science* **106**, 130 (1947); **107**, 569 (1948).
3. D. S. Rassmussen-Taxdal, G. E. Ward, F. H. J. Figge, *Cancer* **8**, 78 (1955); G. E. Moore, *Diagnosis and Localization of Brain Tumors* (Thomas, Springfield, Ill., 1953).
4. D. P. Rall *et al.*, *J. Natl. Cancer Inst.*, in press.

5. Details of the biological phase of the research are in preparation.
6. The generous supply of the tetracycline antibiotics provided by Lederle Laboratories Division of the American Cyanamid Co., and Chas. Pfizer and Co., is hereby gratefully acknowledged.
7. Model SC-5041, Hanovia ultraviolet light, Hanovia Chemical and Manufacturing Co., Newark, N.J. (366 mμ).
8. Visking Corp., Chicago, Ill.
9. The completion of dialysis at this time was shown by the fact that further dialysis yielded no more precipitate of the fluorophore when the dialyzate was made alkaline.
10. J. H. Boothe *et al.*, *J. Am. Chem. Soc.* 75, 4621 (1953); L. H. Conover *et al.*, *ibid.* 75, 4622 (1953).
11. Cary recording spectrophotometer, model 14 PM, Applied Physics Corp., Pasadena, Calif., was used in this work.
12. The blank itself showed no absorption between 350 and 400 mμ.
13. E. I. Rabinowitch, *Photosynthesis* (Interscience, New York, 1951), vol. 2, pt. 1, p. 707.
14. T. Berti and L. Cima, *Boll. ist. sieroterap. milan.* 33, 643 (1954).
15. T. L. Loo, E. D. Titus, D. P. Rall, in preparation.

7 May 1957

Prevention of Toxicity of Amethopterin for Sarcoma-180 Cells in Tissue Culture

The present paper is a preliminary report on the finding that sarcoma-180 (S-180) cells grow normally when the function of folic acid is prevented by amethopterin (Methotrexate), if the medium is supplemented with products of the biosynthetic reactions dependent on folic acid cofactors. It is known that certain microorganisms which require folic acid for growth—for example, *Streptococcus faecalis* 8043—can grow in the absence of this vitamin in a medium containing thymine and adenine or guanine (*1*). That folic acid is one of the nutritional requirements for the growth of mammalian cells in tissue culture was shown by Eagle (*2*). The inhibition of the growth of sarcoma-180 cells in such a medium by amethopterin has been demonstrated (*3*).

The techniques of Eagle (*2, 4*) were used. The medium contained 5 percent thoroughly dialyzed horse serum. The cells were grown in the experimental media for 7 days. The growth of the cells in the presence of amethopterin in a medium containing hypoxanthine, thymidine, and glycine is shown in Table 1. Disintegration of the cells occurred if hypoxanthine or thymidine was omitted from the mixture. In the absence of glycine, some growth was observed, indicating either a small amount derived from the dialyzed horse serum or some formation of glycine, possibly from the exogenous L-threonine (*5*). When glycine was added to this medium, the growth was comparable to that of the control. The complete mixture fully supported the growth of sarcoma-180 cells even in the presence of amethopterin at concentrations 10,000 times that ordinarily required for complete inhibition (Table 1). In body fluids, the concentrations of such compounds could be critical to the effectiveness of amethopterin on neoplastic cells *in vivo*. Similar compounds in the crude medium (chicken plasma clot) might also explain the failure of amethopterin to inhibit sarcoma-180 cells, as reported by Biesele (*6*).

When the function of folic acid was prevented by amethopterin, it was found that sarcoma-180 cells were able to utilize adenine, adenosine, deoxyadenosine, hypoxanthine, and inosine equally well; guanosine supported slower growth of sarcoma-180 cells under these conditions; that is, there was only a threefold increase in 7 days, whereas xanthine and xanthosine were inactive. These results indicate that some "adenine" was derived from guanosine, but the extent to which "guanine" or "adenine," or both, were derived from xanthine and xanthosine was insignificant.

In the presence of amethopterin, thymidine, and glycine, the cells disintegrate if purines are not supplied in the medium (Table 1). Under such conditions it is unlikely that purine synthesis *de novo* occurs. Thus, the single purine in the medium must serve as the sole source, not only of adenine and guanine of nucleic acids, but also of all the coenzymes containing purines as structural constituents. Accordingly, this technique appears to be useful for the study of the pathways of purine metabolism. The present work demonstrates for the first time that mammalian cells (sarcoma-180) are fully capable of using exogenous purines for growth and multiplication.

Further work demonstrated that thymidine could be replaced by thymidylic acid for the growth of sarcoma-180 cells in the presence of amethopterin, glycine, and a purine, but thymine and thymine-riboside had no activity in this respect. A mixture of thymine and deoxyadenosine did not replace a mixture of thymidine and adenine, indicating that this type of transdeoxyribosidation did not occur.

It is seen that the presence of amethopterin creates new requirements for the growth of the tumor cells *in vitro*. When these requirements are met by preformed purines, thymidine, and glycine, inhibition of growth might still be achieved if the utilization of even one of these compounds were prevented. Logical combinations for chemotherapy are thus suggested. The new requirements created by amethopterin probably differ in different species and tissues. It is already known that differences exist in the abilities of various tissues and species to utilize preformed purines *in vivo* (*7*). In addition, rabbit fibroblasts, unlike sarcoma-180 cells, require exogenous L-serine for growth in tissue culture (*8*).

Table 1. Growth of sarcoma-180 cells in tissue culture in the presence of amethopterin. Folic acid (pteroylglutamic acid) was present at a concentration of $2 \times 10^{-7} M$.

Varied supplements in the medium				Degree of cellular multiplication†
Amethopterin* (M)	Hypoxanthine $3 \times 10^{-5} M$	Thymidine $3 \times 10^{-5} M$	Glycine $1 \times 10^{-4} M$	
0				5.7‡
3×10^{-8}				0.70
3×10^{-7}				0.34
3×10^{-7}	+	+	+	5.7§
3×10^{-4}	+	+	+	6.1
3×10^{-7}		+	+	0.60
3×10^{-7}	+		+	0.43
3×10^{-7}	+	+		1.8

* 4-Amino-10-methyl-pteroylglutamic acid.
† Referred to inoculum as 1; determined by the method of Oyama and Eagle (*11*); correlation of the protein determinations with cell counts is discussed by Oyama and Eagle (*11*).
‡ Control.
§ The culture has been carried for 3 weeks under these conditions and is being maintained.

Thymine or thymidine increased the rate of the development of amethopterin resistance in *Streptococcus faecalis* 8043 (*9*). The effect of similar factors on the development of amethopterin resistance in mammalian cells is under study (*10*).

MAIRE T. HAKALA
Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

References and Notes

1. E. E. Snell and H. K. Mitchell, *Proc. Natl. Acad. Sci. U.S.* 27, 1 (1941).
2. H. Eagle, *Science* 122, 501 (1955).
3. ——— and G. E. Foley, *Am. J. Med.* 21, 739 (1956).
4. H. Eagle, *J. Biol. Chem.* 214, 839 (1955); H. Eagle *et al.*, *Science* 123, 845 (1956).
5. H. L. Meltzer and D. B. Sprinson, *J. Biol. Chem.* 197, 461 (1952).
6. J. J. Biesele, *Ann. N.Y. Acad. Sci.* 58, 1129 (1954).
7. C. Heidelberger, *Ann. Rev. Biochem.* 25, 589 (1956); L. L. Bennett and H. E. Skipper, *Arch. Biochem. and Biophys.* 54, 566 (1955).
8. R. F. Haff and H. E. Swim, *Federation Proc.* 15, 591 (1956).
9. M. T. Hakala, *Suomen Kemistilehti* 28, 30 (1955).
10. The study reported here was supported in part by the Dorothy H. and Lewis Rosenstiel Foundation.
11. V. I. Oyama and H. Eagle, *Proc. Soc. Exptl. Biol. Med.* 91, 305 (1956).

22 May 1957

Gastric Secretagogue Effect of Lysine Monohydrochloride

There have been recent references in medical literature to the use of lysine monohydrochloride as a nutritional supplement (*1*). Certain clinical responses, such as increase of appetite, weight gain, and rapid restoration of hemoglobin values, have been reported. Such effects might be produced by either or both of these mechanisms: (i) correction of pre-

existing lysine deficiency and (ii) pharmacodynamic properties of lysine. In an attempt to evaluate what influence the ingestion of lysine has on human physiology, we have undertaken a number of studies. The one reported here concerns the influence on gastric secretion.

Twenty-one adult volunteers were given two test meals each, the first consisting of bread and water and the second of an equal amount of bread and water with 5 g of lysine monohydrochloride added. The two meals were separated by an interval of 1 week. Fractional gastric analysis followed each test meal, and the amounts of free hydrochloric acid and pepsin were determined in samples taken every 15 minutes for 1 hour. The methods used for these analyses are those described by Hawk, Oser, and Summerson (*2*).

The significance of all figures obtained by analysis was determined by t and P values obtained from the formula

$$t = \frac{M_1 - M_2}{\sqrt{(\text{S.E.}_1)^2 + (\text{S.E.}_2)^2}}$$

Values of P are charted from Fischer's table. Values are considered significant when the P value is less than .01.

Eighteen of the 21 subjects showed significant differences of gastric secretions after the two test meals. Whenever the addition of lysine was accompanied by an alteration, the change was an increase. The mean values of all data are given in Table 1. The incidence of effects on pepsin and hydrochloric acid secretion together or separately is as follows: increased pepsin and increased HCl, 12 subjects; increased pepsin but no increase of HCl, three subjects; no increase of pepsin but increased HCl, three subjects; no increase of pepsin or HCl, three subjects.

The addition of 5 g of lysine monohydrochloride to a bread and water test meal significantly increased gastric secretion of hydrochloric acid and pepsin, or both, in 18 of 21 subjects studied. Further work is being done to explain and localize this action. It may be of some significance that previous work has developed evidence that amino acids, either by action in the intestinal tract (*3*) or when given intravenously by systemic action (*4*), promote gastric secretion. The present study may indicate that part of the effect of lysine given as a nutritional supplement results from the stimulation of gastric secretion. This, of course, does not preclude or compete with any importance which lysine may have as a participant in anabolic processes (*5*).

Table 1. Effect of addition of lysine monohydrochloride to diet.

Time (min)	Mean values (units)		Difference	
	No lysine	With lysine	Mean	S.E.*
	Hydrochloric acid			
15	3.7	2.5	−1.1	1.12
30	13.4	24.2	10.8	5.95
60	13.7	33.7	20	2.07
	Pepsin			
15	−48	5	53	2.31
30	1	102	101	5.35
60	30	169	139	8.51

* The standard error was determined from the formula $\sqrt{\frac{(\text{SD}_1)^2}{N} + \frac{(\text{SD}_2)^2}{N}}$

ARTHUR M. SACKLER
LAWRENCE H. SOPHIAN
van Ophuijsen Institute, New York, New York

References and Notes

1. A. A. Albanese *et al.*, *Am. J. Clin. Nutrition* **3**, 121 (1955); *N.Y. State J. Med.* **55**, 3453 (1955); B. Sure, *Am. J. Clin. Nutrition* **4**, 211 (1956).
2. P. B. Hawk, B. L. Oser, W. H. Summerson, *Practical Physiological Chemistry* (Blakiston, Philadelphia, ed. 12, 1948).
3. B. P. Babkin, *Die aeussere Sekretion der Verdauungsdreusen* (Springer, Berlin, 1928).
4. J. La Barre and P. Destree, *Arch. intern. physiol.* **41**, 490 (1935).
5. This project was supported by a grant from E. I. du Pont de Nemours Co., Wilmington, Del.

15 April 1957

Delayed Pain as a Peripheral Sensory Pathway

The existence of "second pain" as a "genuine sensory phenomenon" was recently questioned (*1*). There was also the more interesting implication that a delayed type of "C-fiber pain" does not exist at all as a separate pain sensation. "Double pain" can be aroused by an appropriate noxious stimulus if it is applied to the skin far enough from the central nervous system (*2, 3*). The "second" or slower pain is felt at a distinct time interval after the first or fast component, and it is usually qualitatively different from the first, being more a diffuse ache than a sharp prick, more unpleasant, longer lasting, and like the pain that is aroused from deeper structures below the skin (*4*). Landau and Bishop (*4*) point out that this delayed type of pain has a greater threshold for most types of stimuli than does sharp pricking pain, although its threshold is lower for certain stimuli. They also present evidence (evidently missed by Jones) that the delayed pain sensation can be masked by the faster sharp pain; this makes it difficult to detect double pains under certain conditions of stimulation.

I suggest, therefore, that what the experimental work reported by Jones (*1*) amounts to is a careful description of some conditions of stimulation in which second pain is not demonstrable. For example, threshold electric stimuli will never elicit second pain, even in "480 separate determinations," if those receptors and nerve fibers subserving fast pain are electrically more excitable than those subserving slow pain sensations. The more slowly conducting, amyelinated C fibers, as well as their receptor endings (*4*), have a higher electric threshold than any other nerve-fiber group.

Jones concluded that second pain, when it does appear, is an experimental "artifact" rather than a "genuine sensory phenomenon." These distinctions have little meaning without careful definition for this context. Jones' main contention would appear to be that if a noxious stimulus were delivered at the same instant to any of the receptors that subserve pain, only a fast single, and not a double, pain could be produced—that is, that there is only one type of pain-sensory system; but her negative results do not prove this. If it is difficult [although not impossible (*4*)] to find a stimulus which excites the receptors that subserve slow pain without also exciting other types of receptors, this difficulty cannot be used as proof that slow pain is not a "genuine" and distinct sensory modality. More definitive evidence on this point must be sought from other experimental procedures. It is important, therefore, to analyze some of the criticisms (*1, 5*) of these other, more positive lines of evidence.

Although the total reaction time for perception of pain is obviously not a measure of conduction time, the *increase* in reaction time found when the stimulus is moved to a more distal point (*2*) can be a measure of conduction velocity in the sensory fibers. Jones dismisses such evidence by citing a more recent report (*6*) to show that the increase in reaction time with a more distal stimulus is small and relatively insignificant. But this negative finding concerned touch sensations, not pain (*7*). If the impulses that are responsible for touch sensation are transmitted in group A fibers of even the small variety, for example, at 10 m/sec, then the increase in reaction time that could be expected when the stimulus is moved 50 cm distally would be only 0.05 second, and difficult to detect. On the other hand, if delayed pain is mediated by C fibers, at 1 m/sec, the difference in reaction time would be 0.5 second. This interval, which is easily detectable, was found to be the actual difference in reaction time to slow pain for the conditions stated (*2*).

Although all cutaneous senses show an increasing delay in perception during

compression ischemia (*1, 8*), the delay in perception of pain tends to increase rather suddenly and at a time when touch sensibility is lost (*9*). Zotterman explained this plausibly as follows: fast pain impulses are transmitted along with touch impulses in the A-fiber group, and since the A group ceases functioning before the C group during ischemia, one is left rather suddenly with only slowly conducted, C-fiber, "second-pain impulses." There is general agreement (*3, 4, 8–10*) that after the loss of other sensations has occurred during compression block, a slow, very unpleasant, aching pain sensation can still be aroused or even becomes more evident or "unmasked."

This, and the reverse finding with partial procaine block (that is, abolition of the slow, aching pain with retention of the sharp, pricking pain), also means that the functional pathways for the two types of pain are separable. The suggestion (see *11*) that various pains are simply the result of sufficiently intense activity in any sensory pathway cannot have general validity, since impulses at high frequencies in large numbers of the larger myelinated fibers in a nerve trunk lead only to a tingling sensation without pain (*12*). The common factor with intense tissue stimulation of any kind is tissue damage, and apparently this is the stimulus to which the receptor endings of the "pain fiber" systems are especially sensitive (see also *4*).

The work of the Oxford group (*5, 8*) is cited by Jones to show that the earlier evidence (*3*) for the separability of fast and slow pain, based on the order of loss of sensation during nerve blocks, now appears to have been unreliable. But a careful examination of these papers reveals that this conclusion may not be warranted, although admittedly their general summary statements apparently agree with Jones' evaluation. Sinclair and Hinshaw (*8*) state that they did in fact find statistically significant differences in the order of sensory loss between procaine block and compression block of a given nerve. They also point out some of the factors which could have accounted for the variability of results in their human sensory experiments, when compared with the consistent orders of fiber sizes blocked in animal experiments. Other factors that may account for this variability have been suggested (*4*), to which one may also add that of variation in available tissue buffers which neutralize procaine hydrochloride to the more penetrative free alkaloid. Consistent, clear-cut orders of sensory losses can be obtained by using more dilute procaine solutions on smaller peripheral nerves (*4*) and in spinal anesthesia (*13*), where the sheaths of the spinal rootlets are also uniformly thin.

The apparent failure of histological specificities in receptor end-organs to account for the different sensory modalities found in a given area of skin (*14*) simply shows that the common textbook conception of the correlation between four types of receptor end-organs and four cutaneous sensory modalities is too rigid. Surely, physiological specificities for responses to different stimuli may still exist, even among apparently uniform receptor nerve endings, based on structural and chemical specificities that are not evident with present histological techniques.

Thus, the simplest and best supported hypothesis available, among those hypotheses that have been proposed for relating the pain modalities to the sensory nerve fibers (and one still held fairly widely among physiologists) maintains (i) that pain in general is mediated predominantly by small myelinated (delta) and amyelinated (C) sensory fiber groups and (ii) that, in the skin tissues, fast, sharp pain is mediated predominantly by the first fiber group, while the slow, more unpleasant pain is mediated predominantly by the second. Sensations other than pain are, of course, not necessarily excluded from being represented in these fiber groups (*3, 8*), nor is the possibility excluded that the total pattern of impulses arriving in different peripheral pathways may affect the nature of the subjective sensation that results. In deeper tissues (periosteum, muscle sheaths, and so forth) the more unpleasant pain, without sharpness, is apparently mediated by both groups of small fibers, although even here the C fibers probably are responsible for the slower, more penetrating, longer-lasting component (*4*).

BENJAMIN LIBET*
Department of Physiology,
University of California Medical School,
San Francisco

References and Notes

1. M. H. Jones, *Science* 124, 442 (1956).
2. T. Lewis and E. E. Pochin, *Clin. Sci.* 3, 67 (1937).
3. H. S. Gasser, *Research Publs. Assoc. Research Nervous Mental Disease* 23, 44 (1943).
4. W. Landau and G. H. Bishop, *Arch. Neurol. and Psychiat.* 69, 490 (1953).
5. D. C. Sinclair, *Brain* 78, 584 (1955).
6. P. P. Lele, D. C. Sinclair, G. Weddell, *J. Physiol. (London)* 123, 187 (1954).
7. P. P. Lele and D. C. Sinclair [*J. Neurol. Neurosurg. Psychiat.* 18, 120 (1955)] also drew similar conclusions for reaction time to thermal stimuli, but since their paper did not report any experiments on change in reaction time with different distances of the stimulus from the central nervous system, it is not relevant to the present argument.
8. D. C. Sinclair and J. R. Hinshaw, *Brain* 73, 224, 480 (1950).
9. Y. Zotterman, *Acta Med. Scand.* 80, 185 (1933).
10. T. Lewis and E. E. Pochin, *Clin. Sci.* 3, 141 (1937); J. W. Magladery, D. B. McDougal, Jr., J. Stoll, *Bull. Johns Hopkins Hosp.* 86, 241 (1950); B. Libet, unpublished.
11. J. P. Nafe, *Psychol. Rev.* 49, 1 (1942); F. Schiller, *Arch. Neurol. Psychiat.* 72, 203 (1956).
12. I. M. Thompson *et al., Univ. Calif. (Berkeley) Publs. Anat.* 1, 167 (1934).
13. S. J. Sarnoff and J. G. Arrowood, *Surgery* 20, 150 (1946).
14. D. C. Sinclair, G. Weddell, E. Zander, *J. Anat.* 86, 403 (1952).

* On leave during 1956–57 as a fellow of the Commonwealth Fund of New York, at the Australian National University, Canberra. I wish to acknowledge the aid that participation in the Pain Group of the Lower-Extremity Amputee Research Project, University of California, San Francisco, provided in the writing of this report.

27 May 1957

In my original paper (*1*), the conclusions presented were based on the evidence. Detailed consideration of each bit was impossible because of limitation of space. The foregoing discussion by Libet adds nothing new. It is a restatement of a selected portion of older literature, most of it useless because of failure to control stimulation and because of ignorance of proper conditions of judgment and psychophysical methods (*2*).

The loose accusation that I missed the point that "fast pain" may mask "slow pain" (*3*) is unjust, for it is *specifically* referred to in paragraph eight (*1*). It is a mere assumption, without a shred of evidence to support it, invented to bolster a popular hypothesis. Even the authors could not get most of their "unprejudiced" subjects to feel "second pain."

Space permits comment on only two specific points. The statement that "slow pain" has a higher threshold than "fast pain" is, again, an assumption. It is a conclusion drawn from the fact that abnormally functioning tissue (*4*) has a higher threshold than normal tissue, and so do C fibers. The connection between the two is *at present* without evidence. In my experiment, suprathreshold mechanical stimuli were used without arousing "slow pain." Suprathreshold electric stimuli create serious problems.

Second, Libet's emphasis on reaction time is unfortunate. None of the studies meet the minimum requirements for work in this field (*5*). The negative finding with respect to touch (*6*), the result of much more careful study than the earlier studies on pain, was cited to instill caution in dealing with pain, where the time of action of the stimulus is indeterminate. A difference of 50 milliseconds is, incidentally, readily demonstrable with proper techniques.

Dependence on results of ischemia or blocking, or both, is unwise (*4*). Also, plots of decrease in impulse amplitude and increase in latency against duration of ischemia show *smooth* curves (*7*). Likewise, no correlation was found between conduction time and blocking time [for various touch fibers, and presumably also for others (*8*)].

MARGARET HUBBARD JONES
Department of Psychology,
University of California, Los Angeles

References and Notes

1. M. H. Jones, *Science* 124, 442 (1956).
2. See "Principles of judgment," in J. P. Guilford, *Psychometric Methods* (McGraw-Hill, New York, ed. 2, 1954), chap. 12.
3. W. Landau and G. H. Bishop, *Arch. Neurol. and Psychiat.* 69, 490 (1953).
4. Tissues under progressive compression ischemia, pressure block, and so forth are *not* either perfect or dead. There is interference with normal physiological functioning, the nature of which is unknown.
5. R. S. Woodworth and H. Schlosberg, "Reaction time," in *Experimental Psychology* (Holt, New York, rev. ed., 1954), chap. 2.
6. P. P. Lele, D. C. Sinclair, G. Weddell, *J. Physiol. (London)* 123, 187 (1954).
7. J. W. Magladery, D. B. McDougal, Jr., J. Stoll, *Bull. Johns Hopkins Hosp.* 86, 291 (1950).
8. B. Frankenhaueser, *Acta Physiol. Scand.* 18, 75 (1949).

17 June 1957

An in vitro Effect of Vitamin D on Citrate Oxidation by Kidney Mitochondria

The possibility that an *in vitro* effect of vitamin D may be demonstrable appears evident from the effects on citrate metabolism which have been reviewed in recent publications (*1, 2*). In these it was reported that additions of vitamin D to rachitogenic and nonrachitogenic diets reduced the oxidation of citrate by kidney homogenates and mitochondria, thereby accounting for an increase in the citrate content of certain tissues and an increase in the citrate excretion in urine. Lately, we have succeeded in demonstrating a reduction in citrate oxidation by kidney mitochondria when vitamin D was added *in vitro*.

Young, male rats of the Sprague-Dawley strain were made vitamin-D deficient by the feeding of either a rachitogenic or a nonrachitogenic diet as described earlier (*1*). They were killed by decapitation, and kidney mitochondria were prepared, essentially by the method of Schneider (*3*).

Table 1. The *in vitro* effect of vitamin D on the oxidation of various substrates by kidney mitochondria.

Substrate	Without vitamin D (μl O_2)	With vitamin D* (μl O_2)	Decrease (%)
Citrate	85	32	62
Isocitrate	81	28	65
α-Ketoglutarate	75	80	0
Glutamate	69	55	20
Succinate	115	117	0
β-Hydroxybutyrate	35	31	11
Pyruvate plus oxalacetate	88	90	0

* One hundred and twenty-five micrograms of vitamin D_2 in 0.05 ml of propylene glycol per flask; other flasks received 0.05 ml of propylene glycol alone; 0.7 mg of mitochondrial nitrogen was added to each flask.

The oxidations were carried out in a Warburg apparatus at 30°C with air as the gas phase. The incubation mixture, 3 ml in volume, contained 40 μmole of phosphate buffer (*p*H 7.3), 20 μmole of $MgCl_2$, 6 μmole of adenosine triphosphate, 0.08 μmole of cytochrome *c*, isotonic sucrose, and the indicated additions. Forty micromoles of glucose and excess hexokinase (Sigma) were added from the side arm of the flasks to prevent limitation of oxidation by a lack of phosphate acceptor (*4*). All substrates were added in amounts of 15 μmole, except citrate and succinate, which were added at 45 μmole, and oxalacetate, which was added at 10 μmole with an addition of 15 μmole of pyruvate.

When desired, the flask contents, prior to and following incubation, were deproteinized with 10-percent trichloroacetic acid. The filtrates, for the calculation of P/O ratios, were analyzed for P by the method of Lowry and Lopez (*5*). Citrate was determined by the method of Speck, Moulder, and Evans (*6*), and keto acids by the method of Friedmann and Haugen (*7*). Vitamin D and other compounds tested for their effect were added in propylene glycol or occasionally in the ethanol-serum albumin-phosphate buffer suspension of Nason and Lehman (*8*). In all cases, only 0.05 ml of each of these preparations was added to the contents of a flask. Control flasks received an equivalent amount of appropriate carrier.

The comparative effect of vitamin D on the oxidation of various substrates (Table 1) clearly shows that vitamin D had a pronounced effect on citrate and isocitrate oxidation. Its effect on glutamate oxidation was small, but significant, while on the oxidation of α-ketoglutarate, succinate, β-hydroxybutyrate, and on pyruvate in the presence of oxalacetate, it had little or no effect. It is interesting to note that only the triphosphopyridine nucleotide systems are affected if one considers glutamate oxidized by both tri- and diphosphopyridine nucleotide pathways.

Table 2 illustrates the action of vitamin D in reducing citrate oxidation and α-ketoglutarate production while not affecting coupled phosphorylation efficiency to any degree.

In experiments not shown here, vitamins D_2 and D_3, when added *in vitro* in either of the carrier systems used, were equally active in reducing citrate oxidation, while equal quantities of 7-dehydrocholesterol, ergosterol, Δ^7-cholestenol, and cholesterol were inactive. However, it should be noted that in view of the different solubility characteristics of the sterols as compared with vitamin D, the possibility that they did not enter the mitochondria cannot be ruled out.

Table 2. The *in vitro* effect of vitamin D on the accumulation of α-ketoglutarate during citrate oxidation. The values represent an average of at least six determinations.

	Citrate oxidized (μg)	Oxygen consumed (μl O_2)	α-Ketoglutarate accumulated (μg)	P/O
Without vitamin D	630	83	14.4	3.0
With vitamin D_2*	180	46	8.5	2.7

* One hundred and twenty-five micrograms of vitamin D_2 in 0.05 ml of propylene glycol per flask; other flasks received only 0.05 ml of glycol; 0.7 mg of mitochondrial nitrogen was added per flask, and the oxidation was continued for 10 minutes.

The possibility that the resulting accumulation of citrate in kidney, and possibly in other tissues, may be an important factor in calcium transport and deposition appears increasingly alluring. Studies on these phases are in progress, especially with relation to specific enzyme systems.

Hector F. De Luca
Harry Steenbock

Department of Biochemistry, College of Agriculture, University of Wisconsin, Madison

References and Notes

1. H. F. De Luca, F. C. Gran, H. Steenbock, *J. Biol. Chem.* 224, 201 (1957).
2. H. F. De Luca *et al.*, in preparation.
3. W. C. Schneider, *J. Biol. Chem.* 176, 259 (1948).
4. H. A. Lardy and H. Wellman, *ibid.* 195, 215 (1952).
5. O. H. Lowry and J. A. Lopez, *ibid.* 162, 421 (1946).
6. J. F. Speck, J. W. Moulder, E. A. Evans, Jr., *ibid.* 164, 119 (1946).
7. T. E. Friedmann and G. E. Haugen, *ibid.* 147, 415 (1943).
8. A. Nason and I. R. Lehman, *ibid.* 222, 511 (1956).

15 April 1957

Insect Nutrition and Metabolism of Sterols

The importance of cholesterol and related steroids in insect nutrition was first demonstrated in 1935 (*1*), and it is now well established 'that insects in general require a dietary sterol (*2*). The insects' nutritional requirement for sterols is indicative of an inability to synthesize the steroid nucleus, at least in physiologically adequate amounts. This characteristic is in direct contrast to that of the higher animals, in which steroids are apparently synthesized from simple com-

pounds such as acetate (*3*). The specificity of the insect requirement for sterols has been subjected to detailed investigation by a number of workers, and some of the important configurational requirements have been elucidated (*3*).

The metabolism of sterols by insects has been investigated much less intensively than have the nutritional aspects. Noland (*4*) postulated that certain nutritionally inadequate sterols could not be utilized by the insect because they inhibited the esterification necessary for assimilation from the intestinal tract. This hypothesis was not well supported by the results of a study of the structural specificity of sterol esterification *in vitro* by cockroach gut homogenates (*5*). Using larvae of *Callosobruchus chinensis* L. (cow pea weevil), Ishii (*6*) found that both tetrahydrostigmasterol and epicholestanol were nutritionally adequate for larval growth. Analyses of the sterols contained in the tissues of larvae that were fed on diets containing either of these unnatural compounds as the only dietary sterol indicated that the sterol nuclei had not been metabolically altered. Ishii concluded that the larvae were able to utilize tetrahydrostigmasterol without *in vivo* dehydrogenation at C_5 and C_6 and that they could utilize epicholestanol without isomerization of the hydroxy at C_3.

That an animal could be so loosely organized that a variety of sterols could be utilized at a cellular level without first being subjected to metabolic conversion into steroid compounds typical of the tissues seemed highly unlikely to us. A study was, therefore, undertaken of the effect of dietary sterols on tissue sterols in larvae of the confused flour beetle, *Tribolium confusum* Duval (*7*). In these experiments, the beetle larvae were reared from egg to larval maturity on synthetic diets to which known amounts of pure sterols had been added. The sterols used were cholesterol, 7-dehydrocholesterol, dihydrocholesterol, sitosterol, and ergosterol. The basal synthetic diet was composed of sterol-free fibrin, vitamin test casein, soluble starch, inorganic salts, and a mixture of ten B vitamins.

Before analysis, the larvae were held for 24 hours on a sterol-free diet to minimize interference from sterols contained in the gut contents. The larvae were then homogenized and extracted with a 1/1 mixture of acetone and absolute alcohol. Sterols were precipitated with digitonin. A modified Schoenheimer-Sperry reagent was used for color development, and absorbance after 1.5 and 33 minutes was measured at 620 mμ with a Beckman DU spectrophotometer. This procedure allows an estimation of those sterols which develop maximum color at 1.5 minutes (Δ5, 7) and of those that develop color maximum at about 33 minutes (Δ5) (*8*).

In the present study, 7-hydrocholesterol and cholesterol were used as standards for the "fast" and "slow" sterols, respectively. This analytic method does not permit estimation of sterols which either do not precipitate with digitonin or do not develop color with the Schoenheimer-Sperry reagent. In order to characterize further the "fast" and "slow" sterols found in the tissue extracts, and in order to detect sterols not detectable by the chemical method, a paper chromatographic method was employed. The method of McMahon *et al.* (*9*) was modified for this purpose. Whatman No. 1 filter paper was used, with antimony pentachloride in chloroform as the chromogenic agent. The method was standardized, employing 7-dehydrocholesterol, cholesterol, sitosterol, and dihydrocholesterol. With an ascending solvent mixture of 13 parts phenol, 30 parts methanol, and 57 parts water applied in one direction and a 14/45/41 mixture in the second direction, a two-dimensional chromatogram was obtained in which the several sterols were clearly separated.

Larvae grown on a natural diet (graham flour) and larvae grown on synthetic diets (each containing one of the pure sterols) were analyzed by both chemical and chromatographic methods. All experiments were replicated three times, and all analyses were run in duplicate. In every case, the principal tissue sterol present was a "fast" sterol which, by both its rate of color development with the Schoenheimer-Sperry reagent and its position on the paper chromatogram, was indistinguishable from 7-dehydrocholesterol. Regardless of the identity of the dietary sterol, this tissue sterol was present at concentrations between 850 and 900 μg/g of tissue. In all larval samples, a second sterol was also found, in amounts from 410 to 450 μg/g, and was chemically and chromatographically indistinguishable from cholesterol. No other tissue sterols were detected in amounts that permitted reasonably good identification. Chemical and chromatographic analyses of larvae from the different diets showed no differences attributable to the identity of the sterols in the diets.

Experiments were also set up in which beetle larvae were started on synthetic diets containing either no sterol or one of the nutritionally inadequate sterols, such as calciferol, progesterone, and testosterone. On these diets, however, no larval growth occurred, and none of the insects could be recovered and analyzed. Dihydrocholesterol diets did not promote optimum larval growth, although sufficient numbers of larvae were obtained to run the required analyses.

The results obtained in this study clearly indicate that *Tribolium confusum* larvae can metabolize dietary sterols to the extent of altering the side chain and the degree of saturation in the B ring of the nucleus. The nutritional adequacy of different steroid compounds is probably determined largely by the ability of the insect tissues to convert them into cholesterol and 7-dehydrocholesterol or compounds so closely related to these that they could not be distinguished from them by the methods employed in this study.

STANLEY D. BECK
GEETA G. KAPADIA
Department of Entomology, University of Wisconsin, Madison

References and Notes

1. R. P. Hobson, *Biochem. J.* (*London*) **29**, 1292 (1935).
2. H. Lipke and G. Fraenkel, *Ann. Rev. Entomol.* **1**, 17 (1956).
3. E. C. Albritton, *WADC Tech. Rept. No. 52* (1953); G. Fraenkel and M. Blewett, *Biochem. J.* (*London*) **37**, 692 (1943); H. McKennis, *J. Biol. Chem.* **167**, 645 (1947); and many others.
4. J. L. Noland, *Arch. Biochem. and Biophys.* **52**, 323 (1954).
5. J. E. Casida, S. D. Beck, M. J. Coles, *J. Biol. Chem.* **224**, 365 (1957).
6. S. Ishii, *Bull. Natl. Inst. Agr. Sci.* (*Japan*) **C5**, 29 (1955).
7. This study was supported in part by the National Institutes of Health, and has been approved for publication by the director of the Wisconsin Agricultural Experiment Station.
8. P. R. Moore and C. H. Baumann, *J. Biol. Chem.* **195**, 615 (1952).
9. J. M. McMahon, R. B. Davis, G. Kalnitsky, *Proc. Soc. Exptl. Biol. Med.* **75**, 799 (1950).

23 May 1957

Cytolysis versus Differentiation in Antineurula Serum

Complex antigenic mixtures derived from various developmental stages of *Rana pipiens* are being studied (*1*) in an analysis of the chemical patterns of ontogeny (*2*). Antigens were prepared from entire neurulae (Shumway stages 14 and 15) by a standardized homogenization in a Ten Broek tissue grinder with 0.05*M* phosphate-buffered saline at *p*H 7.4, and collection of the supernatants following centrifugation at 1500 *g* with final clearing at 10,000 *g* (*3*). Such supernatants, containing 1.6 to 2.0 mg of total N per milliliter, were emulsified (*4*), and quantities containing 0.2 ml of the antigenic mixture were injected under each scapula of four American chinchilla rabbits. Antisera were collected at periodic intervals and screened, using the interface precipitin reaction and the Ouchterlony agar diffusion technique (*5*). A representative antiserum, collected 4 months after injection, yielded a positive antigen dilution titer at 0.2 μg of N per milliliter. Similar titers were obtained with γ-globulin fractions prepared by a cold ethanol

Table 1. "Dorsal tissues" of *Rana pipiens* neurulae cultivated in serologic media. Data refer to numbers of cultures. Numbers in parentheses: first number, number of rabbits; second number, number of sera. The minus signs in column 2 indicate that no precipitate formed.

Sera	Condition of cultures at 7 days, 20° to 24°C				
	Precipitate	Lysis	Poor	Normal	Total
Normal rabbit serum (4–4)	−	3	27	27	57
Antineurula supernatant (4–7)	+	91	5	0	96
Normal rabbit β-globulin (2–2)	−	0	2	18	20
Antineurula supernatant β-globulin (1–2)	±	0	28	5	33
Normal rabbit γ-globulin (2–2)	−	0	2	33	35
Antineurula supernatant γ-globulin (2–3)	+	57	8	0	65
Antineurula supernatant (1–5), crude and γ-globulin, absorbed with					
Neurula supernatant	−	0	40	27	67
Neurula pseudoglobulin	+	0	49	0	49
Neurula vitellin	+	32	5	0	37

method (*6*) which was controlled by microelectrophoretic analysis (*7*).

Fragments of dorsal trunk tissues, obtained from stage-15 neurulae, which contained medullary plate, neural crest, notochord, dorsal mesoderm, and, occasionally, epidermal elements, were cultured singly in hanging drops of Niu-Twitty balanced salt medium plus 10 units of penicillin and 1 μg of streptomycin per milliliter. After 7 to 14 days, these normal cultures contained chromatophores, neuroblasts, chorda, fibroblasts, striated fibroblasts, mesenchyme, and, occasionally, ciliated epidermal cells. Similar cultures (Table 1) were made in media containing crude normal rabbit sera, crude antineurula supernatant sera, normal rabbit β- and γ-globulin, and antineurula supernatant β- and γ-globulin which had previously been dialyzed against Niu-Twitty medium. These media contained rabbit protein in amounts varying between 4.5 and 0.7 percent. Control tests at varying dilutions of these reagents indicated that the nature of the results was independent of the rabbit protein concentration per se within this range.

In Table 1, tabulations for undifferentiated but living cultures and cultures showing only epidermal and mesenchymal differentiation are reported together under the heading "poor." Some as yet unknown factors in normal rabbit sera were mildly toxic (undifferentiated, 8 cases; epidermal and mesenchymal differentiation, 19 cases). However, development in normal γ-globulin was identical with that shown in Niu-Twitty control cultures. The crude antisera and their γ-globulins were potent cytolytic agents, while their β-globulins showed some toxicity (undifferentiated, 10 cases; epidermal and mesenchymal differentiation, 18 cases). This cytolytic activity was independent of complement, which, in initial tests, was destroyed by heating at 56°C for 30 minutes. These observations on *Rana pipiens* are in close agreement with those made by one of us (*8*) on *Hynobius nigrescens,* also using antineurula supernatant in tissue cultures.

In a further examination of specificity, these antisera were absorbed with a number of reagents. Among these were the water-soluble (pseudoglobulin or livetin) and water-insoluble (vitellin) proteins obtained (*3*) from repeatedly washed neurula yolk platelets.

The various line patterns (Fig. 1, *a, b,* and *c*) found in agar diffusion analyses of unabsorbed and absorbed antisera will be identified in another context; however, attention is invited to the line labeled *c*. In spite of differences in its rate of diffusion in the complex mixture and purified system, it was found to be continuous between the wells containing the homologous reagent and the pseudoglobulin in appropriately oriented plates —a condition which suggests identity (*9*). This identity is supported by the absence of the line in patterns produced by the absorbed antisera. Other types of pseudoglobulin preparations produced two lines with these antisera, one of which was identical to line *c*. This fits well with other evidence (*10*).

It may be seen in Table 1 that absorption with pseudoglobulin removed all the cytolysis observed with the unabsorbed antisera. Some level of cellular differentiation was possible (undifferentiated, 27 cases; epidermal and mesenchymal differentiation, 22 cases) even in the presence of precipitate from other serologic systems. However, this differentiation remained at a much lower level than that in the unabsorbed (normal rabbit serum: undifferentiated, 8 cases; epidermal and mesenchymal differentiation, 19 cases) or neurula supernatant absorbed (undifferentiated, 2 cases; epidermal and mesenchymal differentiation, 38 cases) controls as measured by the variey of cell types which developed.

Antisera absorbed with vitellin retained the cytolytic activity of the unabsorbed antisera. This corresponds with earlier evidence of the serologic nonidentity of pseudoglobulin and vitellin (*3*) and must be taken into account in considerations of the functional relationships of these materials (*10, 11*). Certainly this nonidentity is dependent on more extensive molecular changes than those implied in a conversion of vitellin to pseudoglobulin by dephosphorylation alone (*12*).

These experiments suggest that the cytolytic activity of antineurula sera can be referred to one or more antigenic systems represented among the serologically active groupings on pseudoglobulin and may provide a model to explain inconsistencies in the cytolytic activity of various sera as reported in the literature (*2*). The low level of differentiation obtained after absorption with pseudoglobulin suggests that other antigenic factors (Fig. 1, *a* and *b*) are more closely related to differentiation.

It will not be known whether the cytolytic or differentiation-inhibiting activity, or both, is localized in the cell membrane or whether the antibody penetrates the cell, until fluorescent antibody studies now in progress are completed. The possibility that pseudoglobulin controls certain characteristics of the cell membrane may explain the observations on which the suggestion of its inductive role was based (*12*).

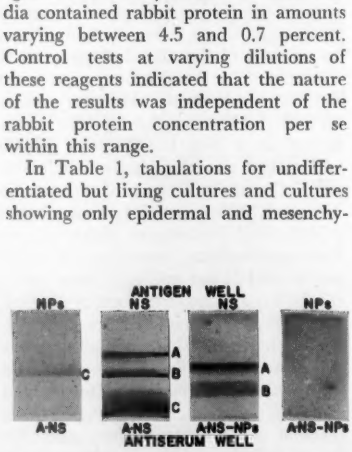


Fig. 1. Agar diffusion patterns with a frog neurula-antineurula system. NPs, neurula pseudoglobulin; NS, neurula supernatant; A.NS, antineurula supernatant; A.NS-NPs, antineurula supernatant absorbed with neurula pseudoglobulin.

GEORGE W. NACE
KAZUKO INOUE*
Zoology Department, Duke University, Durham, North Carolina

References and Notes

1. This investigation was supported by research grant RG 3555 from the National Institutes of Health, U.S. Public Health Service.

2. G. W. Nace, *Ross Lab. Research Conf. on Mental Retardation,* in press; G. W. Nace, *Ann. N.Y. Acad. Sci.* 60, 1038 (1955).
3. R. A. Flickinger and G. W. Nace, *Exptl. Cell Research* 3, 393 (1952).
4. J. Freund, *Am. J. Clin. Pathol.* 21, 645 (1951).
5. M. W. Wilson and B. H. Pringle, *J. Immunol.* 77, 52 (1956); 75, 460 (1955); 73, 232 (1954).
6. H. F. Deutsch, *Methods in Med. Research* 5, 284 (1952).

7. H. J. Antweiler, Kolloid-Z. 115, 130 (1949).
8. K. Inoue, work recently completed in Japan.
9. J. R. Preer, *J. Immunol.* 77, 53 (1956); *J.* Oudin, *Methods in Med. Research* 5, 335 (1952).
10. R. A. Flickinger and D. E. Rounds, *Biochim. et Biophys. Acta* 22, 38 (1956); P. R. Gross and L. I. Gilbert, *Trans. N.Y. Acad. Sci. Ser. II* 19, 108 (1956); O. A. Schjeide, E. Levi, R. A. Flickinger, *Growth* 19, 297 (1955).
11. S. Nass, *Trans. N.Y. Acad. Sci. Ser. II* 19, 118 (1956).
12. R. A. Flickinger, *J. Exptl. Zool.* 131, 307 (1956).
* On leave from the Pathology Department, Medical School, Kanazawa University, and from Kanazawa Women's College, Kanazawa, Japan.

16 April 1957

Thermal Protection of Choline Chloride from Decomposition by Ionizing Radiation

Changes produced by ionizing radiations in target materials—for example, polymerization of vinyl monomers (*1*) and inactivation of enzymes (*2*)—are in general enhanced by temperature elevation. It appears, however, that choline chloride, which at room temperature is one of the most radiosensitive organic solids known (*3*), becomes markedly radiation-resistant at 150°C.

Studies have been carried out at our laboratory (*4*) on the effects of ionizing radiation on nerve tissue constituents, including the cholinesterase system (*5*). Choline, a substance essential to nerve conduction, has been shown (*3*) to decompose by a free radical chain mechanism to trimethylamine and acetaldehyde when it is subjected to ionizing radiation as the pure crystalline chloride. When exposed at room temperature to 2-Mev electrons, Co^{60} γ-rays, or C^{14} β-rays, the *G* values—that is, the number of molecules decomposed per 100 ev—were 20, 175, and 1250 respectively; at −196°C the compound was stable.

In an attempt to determine the energy of activation of the radiation decomposition of choline chloride, the crystalline compound was exposed to Co^{60} γ-rays at room temperature, 50°C, and 150°C. At each temperature, three Pyrex ampules of twice recrystallized choline chloride, dried under vacuum and nitrogen at 110°C for 2 hours and vacuum sealed, were exposed to the radiation for varying periods of time. Three Co^{60} sources were used, two of which (delivering 232,000 and 792,000 rep/hr) were maintained at room temperature; the third (572,000 rep/hr) had a normal operating temperature of 50°C and was equipped with a furnace for higher temperatures. The percentage of remaining choline in each of the irradiated samples and its control was determined by the reineckate method (*6*). The *G* values, which are listed in Table 1, were then calculated for each run from the obtained semilogarithmic relationship between the percentage of remaining choline and the radiation dose in rep.

Decreasing the radiation dose rate or increasing the temperature from 20° to 50°C resulted in higher yields of decomposition. However, at 150°, regardless of the radiation exposure (4.6 to 13.7×10^6 rep) only 9 to 13 percent of the choline decomposed. The nonirradiated control, which was also kept at 150°C, did not change in appearance. The irradiated samples, however, became brown, and a small amount of insoluble material formed.

In view of these changes, it was necessary to determine whether more than one compound was responsible for the very high choline recovery as indicated by the reineckate analyses. Cholinemethyl-C^{14} chloride was synthesized (*3*) and recrystallized twice. The product had a specific activity of 66.5 mμc/mg of choline chloride (*7*) (calculated, 62.5 mμc/mg). It was shown to be chromatographically pure (Whatman No. 1 paper and 4/1/1 *n*-butanol, concentrated HCl, and water, followed by autoradiography). The labeled choline was irradiated at 150°C in the same manner as the nonlabeled material. Once again, some brown and insoluble substances were formed.

Analysis of the soluble material by the reineckate procedure indicated that the choline recoveries following exposure to 1.4, 2.8, and 3.7×10^7 rep were 94, 94, and 93 percent, respectively (*8*). Solutions of the sample which had been irradiated for 64.5 hours at 150°C, and of the labeled control, which also had been held at 150°C for the same length of time, were chromatographed for 23 hours. Included on the same chromatogram were samples of C^{14}-labeled trimethylamine and nonheated, nonirradiated, labeled choline. The heated and nonheated control samples showed a single spot only. The irradiated sample activity was predominantly at the same R_f as the choline controls with only a faint trace (about 1 percent) at a slightly higher R_f. Apparently, therefore, no C^{14}-labeled compound other than choline had contributed to the color developed in the analytic procedure.

It might be assumed that the brown, irradiation-induced materials had acted as inhibitors of the free radical chain degradation of the remaining choline. If this were the case, one would expect that this type of inhibition should have been evident not only at 150°C but also, to some degree, at lower temperatures.

Lemmon (*3*) has suggested that the spatial arrangement of atoms of crystalline choline chloride may play an important role in the free radical chain degradation. One might speculate that thermal excitation at 150°C (in contrast to that at lower temperatures or to the excitation due to ionizing radiation per se) can disturb the arrangement sufficiently to prevent the chain reaction. Further studies, therefore, may help to determine the relationship of crystalline structure to free radical chain reactions in solids, as well as to establish the use of elevated temperatures to protect some labile materials during irradiation.

Table 1. Effect of temperature and dose rate on Co^{60} γ-ray decomposition of choline.

Co^{60} source (rep/hr)	Temp. of irradiation (°C)	Dose causing 50% decompn. (reps)	G values
792,000	18–20	2.9×10^7	143
232,000	20–25	1.0×10^7	415
572,000	50	0.8×10^7	520
572,000	150	*	

* Regardless of the dose—that is, from 0.5 to 3.7×10^7 rep.—approximately only 10 percent of the choline decomposed.

I. Serlin*

Medical Department,
Brookhaven National Laboratory,
Upton, New York

References and Notes

1. D. S. Ballantine and B. Manowitz, *Brookhaven Natl. Lab.* No. 229 (T-35) (March 1953).
2. E. C. Pollard, *Advances in Biol. and Med. Phys.* 3, 153 (1953).
3. R. M. Lemmon, M. A. Parsons, D. M. Chin, *J. Am. Chem. Soc.* 77, 4139 (1955).
4. This work was supported by the U.S. Atomic Energy Commission.
5. I. Serlin and G. C. Cotzias, *Radiation Research* 6, 55 (1957); I. Serlin and D. J. Fluke, *J. Biol. Chem.* 223, 727 (1956).
6. D. Glick, *J. Biol. Chem.* 156, 643 (1944).
7. Determined by D. Christman of the chemistry department, Brookhaven National Laboratory; irradiations in the Co^{60} γ-ray sources were carried out by the staff of the nuclear engineering department.
8. Since the furnace in this Co^{60} source required approximately 15 minutes to either heat up or cool down from 150°C after the addition or removal of a sample, it is possible that the observed small choline losses were initiated in these periods.

* Present address: Shawinigan Resins Corporation, Springfield, Mass.

3 May 1957

Segregation of Plasmagenes and the Determination Problem

Investigations on the willow-herb (*Epilobium*) have shown that the intra-individual segregation of plasmagenes is a basic character of cytoplasmic inheritance (*1*). During vegetative cell divisions the plasmagenes may be distributed accidentally. They may, however, enter more or less exclusively one of the daughter cells as well. In such a way differences of cells and characteristic patterns arise within the plant. Besides the cytoplasmic segregation occurring in

Epilobium, a more generally known example is the distribution of plastids in white-spotted plants. Struck by these phenomena, I have advanced the hypothesis that several processes of determination are caused essentially by an unequal distribution of plasmagenes during somatic development (2).

In this respect, the cytoplasmic alteration "irregulare" (3) offers special interest. "Irregulare" arises either after treatment by radioactive isotopes or spontaneously in certain interspecific hybrids which contain cytoplasm of the race "Essen" of *Epilobium hirsutum*. The "irregulare" character is transmitted nearly constantly through numerous generations only by the mother, even in presence of different nuclei foreign to the cytoplasm. During the ontogenetic development, especially during the development of the leaves, new cytoplasmic alterations are frequently given off by "irregulare" plants. It is in this way that "irregulare" leaf patterns originate. If a new lateral shoot is formed in such an anomalous area, maternal inheritance can be proved by crossing experiments. Therefore plasmonic [*plasmon* means the sum of all extranuclear genes (plasmagenes)] alterations must be involved.

One of the plasmonic alterations that arises frequently from "irregulare" or otherwise by treatment with radioactive isotopes is the alteration "rhytidiophyllum." The leaves or leaf patterns of the altered plants show a more or less strongly wrinkled lamina. By means of anatomical investigation, different causes of this wrinkling have been revealed in various "rhytidiophyllum" plants.

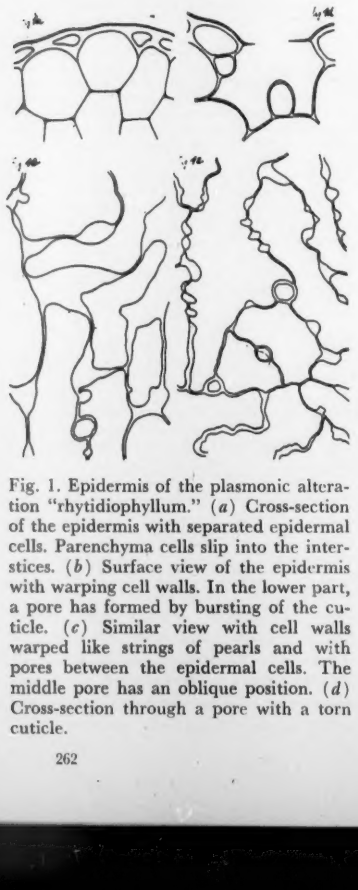


Fig. 1. Epidermis of the plasmonic alteration "rhytidiophyllum." (*a*) Cross-section of the epidermis with separated epidermal cells. Parenchyma cells slip into the interstices. (*b*) Surface view of the epidermis with warping cell walls. In the lower part, a pore has formed by bursting of the cuticle. (*c*) Similar view with cell walls warped like strings of pearls and with pores between the epidermal cells. The middle pore has an oblique position. (*d*) Cross-section through a pore with a torn cuticle.

Within a majority of "rhytidiophyllum" plants the division of epidermal cells soon stops. If this takes place at an early stage of development of the epidermis, the easily warping cell walls become expanded, and the cell bodies are separated. Parenchyma cells slip into the interstices, until they touch the cuticle. In many cases a cuticle covers these different cell types in a normal way. Occasionally it bursts and forms openings, which recall the pores of stomata (Fig. 1). If division of epidermal cells stops later, the development of stomata will be disturbed. Then a single guard cell may develop with a more or less normal slit at its side, or an air chamber below an undeveloped stoma mother cell. In a still later stage the stomata are stretched out into large apertures, below which the parenchyma cells lie open and shrink up. In extreme cases intercellular spaces between the epidermal cells become widened, or individual epidermal cells become torn. Then the epidermis covers the parenchyma only as a perforated net (Fig. 2). In all these cases the "rhytidiophyllum" character is produced by disharmonic development of two independent cell layers.

In some chimeras of "albomaculatum," in which cell division in the white parenchyma ceases early, the epidermis nevertheless continues dividing and lies in high folds. If individual white cells amid normal palisade parenchyma cannot divide, the white palisade cells are stretched out and assume a shape similar to those of the spongy parenchyma. Vice versa, normally dividing green spongy parenchyma cells amid white spongy parenchyma of white-spotted plants assume the shape of palisade cells.

During normal development, the typical shape of the two different parenchymas is essentially determined by their different rates of cell division. The origin of "rhytidiophyllum" disturbances agrees with these observations, and thus one may prove that they are caused by segregation of plasmagenes.

In a second type of "rhytidiophyllum," the epidermal cells do not grow horizontally, but vertically, to the leaf surface. New cell walls are built up periclinally (Fig. 3*a*). Such a multiseriate epidermis slightly resembles the epidermis of some xerophytes.

The third "rhytidiophyllum" type, and that of special interest, was found in relatively numerous plants. In these the cells of the mesophyll are transformed into cells of a new and complete epidermis. In the case of local "rhytidiophyll-

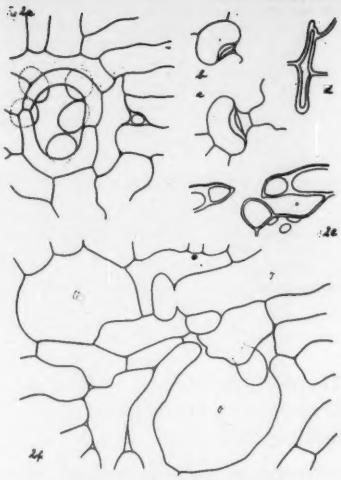


Fig. 2. Epidermis of "rhytidiophyllum." (*a*) Surface view of the upper epidermis of the leaf with one stoma and with intercellular spaces widened by the growing parenchyma. Below the open stoma, some cells of palisade parenchyma are discernible. (*b*) Disturbed stoma with only one guard cell beneath the slit. (*c*) Disturbed stoma; one of the guard cells has not developed. (*d*) Optical section through the air chamber below an undeveloped stoma mother cell. (*e*) Cross-section of a stretched stoma similar to that of *a*. (*f*) Epidermis stretched out to form a net; *o*, openings in the epidermis.

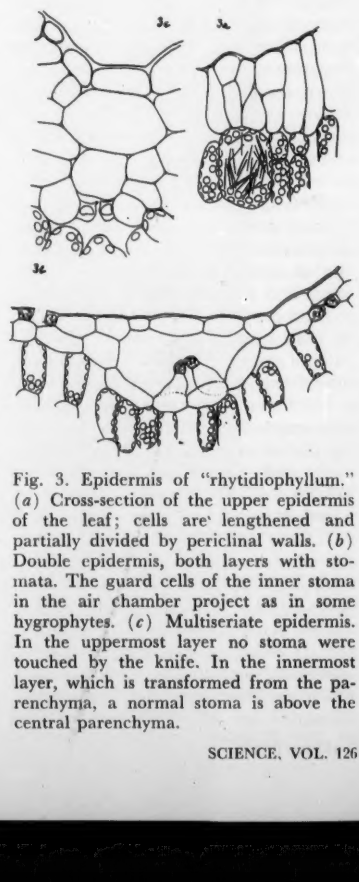


Fig. 3. Epidermis of "rhytidiophyllum." (*a*) Cross-section of the upper epidermis of the leaf; cells are lengthened and partially divided by periclinal walls. (*b*) Double epidermis, both layers with stomata. The guard cells of the inner stoma in the air chamber project as in some hygrophytes. (*c*) Multiseriate epidermis. In the uppermost layer no stoma were touched by the knife. In the innermost layer, which is transformed from the parenchyma, a normal stoma is above the central parenchyma.

lum" patterns, this transformation takes place within relatively late phases of leaf development. If there rises only one second epidermis, it will contain typical stomata and typical mother cells of hairs. In the interior of the leaf, however, these hairs do not develop further. In some cases this second epidermis is situated immediately below the normal one; in other cases it lines the much enlarged air chambers (Fig. 3*b*). In the first instance, the stomata of neither epidermis function. In the second case, the guard cells of the inner epidermis are lifted up under the influence of the high air moisture within the leaf. In most patterns with a double epidermis, one of the chlorenchyma layers is missing.

In some cases most layers of the spongy parenchyma have lost their normal chloroplasts and have changed into an epidermal tissue with intercellular spaces. Stomata were formed at the boundary between this and the normally green parenchyma amid the leaf (Fig. 3*c*). Other similar transformations of palisade parenchyma cannot be identified quite exactly as epidermal tissue because stomata are missing in them.

In the third type of "rhytidiophyllum" the following fact is of greatest interest: a plasmonic alteration, which can be proved as such, does not produce disturbances of normal development as in other cases of cytoplasmic inheritance, but a change of determination takes place. A meristematic tissue that should form chlorenchymatic cells develops instead into epidermal cells. This determination process differs from the normal formation of dermatogen only by the atypical moment of realization and by its abnormal localization. This difference, however, is caused by the time and locality of cytoplasmic segregation. If we start from the well-founded opinion that plasmonic segregation is produced by an unequal distribution of plasmagenes, we then logically arrive at the further conclusion that similar proceedings take place during the determination of the typical dermatogen as well, and that plasmagenes are distributed irregularly during the first cell divisions of the embryo (*4*), in which root and shoot and later on the layers of differentiated tissues are preformed.

Of course, cytoplasmic inheritance, as taking part in the processes of determination, is very difficult to prove by crossing experiments, and in many cases this task is impossible to solve at all. The aforementioned observations, however, show that the hypothesis of the significance of plasmagenes for determination possesses a high degree of probability. This hypothesis can be proved exactly by a more detailed investigation of the behavior of cytoplasm and its inheritance during ontogeny. One then will have to take into account that an analysis of intraindividual patterns is of the same importance for cytoplasmic inheritance as is an analysis of segregating crossings for chromosomal inheritance. Moreover, one should not forget that the fundamental principle of heredity means the identical reproduction and passing on of all genes during vegetative as well as during generative reproduction.

P. Michaelis
F. Bartels

Max-Planck-Institut für Züchtungsforschung, Köln-Vogelsang, Germany

References and Notes

1. P. Michaelis, *Advances in Genet.* **6**, 287 (1954); *Biol. Zentr.* **73**, 353 (1954); *Cytologia* **20**, 315 (1955); *Handbuch der Pflanzenzüchtung* (Parey, Berlin, ed. 2, 1955), vol. 1, pp. 140–175.
2. ———, *Z. Krebsforsch.* **56**, 165, 225 (1948).
3. ———, *Z. Vererbungs.* **83**, 36 (1949).
4. F. Bartels, *Flora* **144**, 105 (1956); *Ber. deut. botan. Ges.* **69**, 375 (1956).

21 June 1957

Role of Fumarate in Formation of Stromata in "Vernalized" Ergot Fungus

It is well known that, for germination of *Claviceps purpurea*, an exposure of several weeks to cold, followed by a short period of exposure at higher temperature, is necessary. According to Kirchhoff (*1*), who studied this question in detail, the effect of cold seems to be similar to that of the vernalization of seeds. In studies of the respiration of germinating sclerotia and fully developed stromata of ergot of rye, I have found that fumarate plays a special role in this process.

The test ergot strain was Hungarian 12. An exposure to 0° to 3°C during 6 weeks was effective, causing 65 to 70 percent of the sclerotia to germinate after 3 weeks at 20°C on a double layer of wet filter paper in petri dishes. The sclerotia that had been treated as described were vacuum infiltrated for 1 hour with distilled water (control) or with $2 \times 10^{-2}M$ fumarate under 20 to 30 mm-Hg pressure. Infiltration with water does not influence the development of stromata, while infiltration with fumarate entirely inhibits the germination. This inhibition can be overcome to some extent by infiltration with $2 \times 10^{-2}M$ succinate. Succinate by itself has no effect on germination.

In order to gain a deeper insight into this question, conventional Warburg respirometers were used for the estimation of oxygen absorption (Q_{O_2}) of the sclerotia and stromata that had been infiltrated with the various compounds described in Table 1. Measurements were carried out on four occasions in triplicate. As shown in Table 1, the fumarate does not inhibit the respiration of sclerotia, while the oxygen consumption of stromata was strongly affected by it. Succinate added in concentrations equal to those of the fumarate is able to renew oxygen uptake to a considerable degree.

Table 1. Effect of fumarate and succinate on the respiration of sclerotia and stromata of ergot fungus.

Infiltration	Q_{O_2}		
	Sclerotia		Stromata
	Control	Cold treated	
Distilled water	25	27	346
Fumarate ($2 \times 10^{-2}M$)	22	25	20
Succinate ($2 \times 10^{-2}M$)	24	26	387
Fumarate + succinate	25	26	276

A consideration of these results has led to the following tentative conclusions and working hypothesis. The respiration of stromata follows a different pathway from that of the sclerotia. An explanation could be given for the inhibitory effect of fumarate on germination by the fact that, in the presence of fumarate, the respiration of stromata is inhibited. On the basis of the compensatory effect of succinate, it may be assumed that an unknown acid metabolism plays an important role in the organization of the stromata of ergot fungus. This is in agreement with the work of Cantino (*2*), who studied the relationship between cellular metabolism and morphogenesis in *Blastocladiella emersonii*.

A. St. Garay*

Research Institute for Medicinal Plants, Budapest, Hungary

References and Notes

1. H. Kirchhoff, *Zentr. Bakteriol. Parasitenk. Abt. II* **77**, 310 (1929).
2. E. Cantino, *Mycologia* **48**, 225 (1956).

* Present address: Institute of Plant Breeding, Fertőd, Hungary.

26 March 1957

Conditioned Inhibition of Respiration and Heart Rate in the Goldfish

Conditioned inhibition of breathing rate and heart rate has been reported for various mammalian species, including man (*1*). Typically, the termination of a light, sound, or some other conditioned stimulus (CS) is repeatedly associated with noxious electric stimulation of some

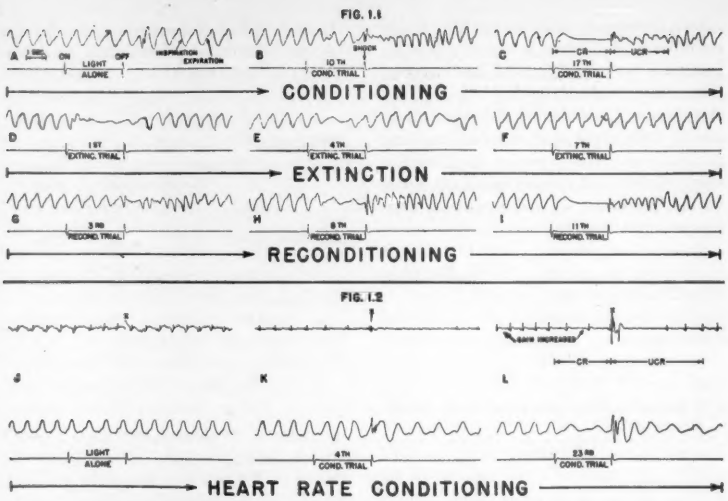


Fig. 1.1. Effect on breathing rate of light alone during preconditioning trials (A); of light paired with shock during conditioning trials (B, C); of light alone during extinction trials (D–F); and of light paired with shock during reconditioning trials (G–I). CR denotes conditioned response to light onset, and UCR denotes unconditioned response to shock. Fig. 1.2 (another fish). Effect on breathing and heart rate of light alone (J) and of light paired with shock (K, L). *X* denotes recording artifacts. Note that both frequency and amplitude of the EKG diminish during presentation of the CS (L). The EKG was recorded with a small time constant of amplification in order to avoid drift.

portion of the organism's anatomy. After sufficient pairings of the CS and shock, the CS acquires the power to elicit a slowing of the heart rate or inhibited respiration, or both, as a conditioned response. The conditioned inhibition disappears (that is, is extinguished) with successive presentations of the CS in the absence of continued shock reinforcement.

Although this has been amply demonstrated in higher forms, little evidence of this sort of conditioning exists for poikilotherms (*2*). The purpose of this report is to demonstrate similar breathing and heart-rate conditioning effects in goldfish (*Carassius auratus*) and to suggest some applications of the conditioning method that we have employed.

In our experiments (*3*), a fish was immobilized in a special clamp (which left the head and operculi free) and was submerged in a small, water-filled tank that was painted flat black. Two sheets of aluminum foil, placed along opposite sides of the tank, served as electrodes. Shock was delivered through the water (and the fish) by discharging, through the electrodes, a 0.3- to 1.0-μf condenser, charged at 45 v (*4*). The shock occurred simultaneously with the termination of the CS, which consisted of a 3- to 7-sec duration change in illumination through the milk-glass bottom of the tank. Two 6-v lamps (one at each end of the tank) were illuminated during the CS interval. The sequence of light-followed-by-shock was automatically timed (Hunter interval timer).

Respiratory movements were mechanically transmitted (by means of a lever arm that rested against one operculum) to a thin sheet of flexible steel (1.5 in. by 3 in.) upon which four strain gages were mounted and wired to form a Wheatstone bridge. The lever arm was soldered to the free end of the flexible steel. Opercular movements were translated into proportional direct-current voltages across the bridge, which was supplied by a 3-v battery. Potential changes were amplified and recorded on one channel of a Grass standard inkwriter; the largest time constant available was used to prevent distortion of the tracings. In some of the experiments, leads from thin steel needles introduced in the region of the heart were coupled to another channel of the inkwriter for recording the EKG. A signal marker recorded onset and termination of the CS. Each subject was permitted from 10 to 30 minutes' adaptation in the tank (that is, until breathing rate had become regular) before each experiment was started.

Figure 1 shows typical results. Figure 1.1 presents recordings from a fish in which respiratory inhibition was first conditioned, then extinguished (by nonreinforced presentation of the CS), and then reconditioned. Figure 1.2 shows the record of another fish in which inhibition of heart rate, as well as respiration, was conditioned.

It has been our experience that goldfish will show the conditioning effects illustrated in Fig. 1 within 15 to 40 trials, spaced from 1 to 2 minutes apart. Of the 30 fish conditioned, 16 showed marked inhibition of breathing within 20 trials, five within 30 trials, three within 40 trials, and six failed to condition reliably within 100 trials (*5*).

Respiratory inhibition does not appear to be a matter of pseudoconditioning or sensitization. Breathing fails to be inhibited by noise or by tactual stimulation after conditioning, and animals fail to show inhibition of respiration at CS onset after backward conditioning (that is, shock presented first, followed by the CS). Also, the reconditioning record of Fig. 1.1 indicates that extinction was not caused by fatigue, ataxia, and the like.

The technique which we have decribed is a convenient, quantitative method for studying the conditioning and retention of breathing and heart-rate inhibition in the goldfish—a readily accessible, inexpensive, and easily maintained species. Preliminary studies suggest that the method may have general application as a screening device for testing the effects of drugs on unconditioned breathing rate and heart rate and on learned emotional responses that involve these measures (*6*). The method, of course, is also suitable for behavioral studies involving the acquisition, retention, and extinction of learned responses in fish.

LEON S. OTIS*
JEAN A. CERF†
GARTH J. THOMAS
Neuropsychiatric Institute, University of Illinois, College of Medicine, Chicago

References and Notes

1. B. J. Freedman, *J. Nervous Mental Disease* 113, 1 (1951); J. M. Notterman, W. N. Schoenfeld, P. J. Bersh, *J. Comp. Physiol. Psychol.* 45, 1 (1952).
2. W. N. Kellogg, *Am. Psychol.* 7, 279 (1952).
3. This work was aided by grant M-694, MH, from the U.S. Public Health Service.
4. A 20- to 25-v square pulse of 0.2-msec duration, delivered at a frequency of 400/sec and on for 0.25–0.50 sec. has been alternately used (Grass stimulator S-4). This stimulus is recommended for chronic preparations.
5. Occasionally fish are found which have a breathing rate so irregular that they are not fit subjects for this sort of conditioning. Also, some fish appear to react to shock stimulation with less disturbance of respiration than others. [see V. I. Gusel'nikov, *Fiziol. Zhur. S.S.S.R.* 38, No. 5, 612 (1952)].
6. Emotional responses are operationally defined here as changes in response measures which attend or follow the onset of a neutral stimulus previously associated with *noxious* stimulation.

* Present address: Department of Psychology, State University of Iowa, Iowa City.
† Chargé de recherches of the Belgian National Foundation for Scientific Research. Permanent address: Laboratoire de Pathologie générale, Faculté de Médecine, Brussels University, Belgium.

26 April 1957

Book Reviews

Selected Papers in Statistics and Probability by Abraham Wald. T. W. Anderson *et al.*, Eds. Published for the Institute of Mathematical Statistics by Stanford University Press, Stanford, California, 1957. ix + 702 pp. $10.

The development of a scientific discipline goes on at an uneven rate. Frequently, whole decades go by without major scientific advances; they are given simply to meticulous efforts aimed at perfecting the domain already covered. Then the monotony of this day-to-day routine is broken by the appearance of an individual of real talent. His papers reveal new ideas, formulate new problems, and break new ground. Occasionally, an old idea is rediscovered—perhaps one formulated long ago by another man of great talent and then overlooked by his contemporaries and forgotten. This old idea appears in a new light and becomes a basis for a new theory.

An incident of this kind recently occurred in the history of statistics. It was connected with the appearance on the scene of Abraham Wald. Born in Rumania and educated in Vienna, Abraham Wald came to Columbia University in 1938. Up to that time his interests had been directed toward various sections of pure mathematics. However, in 1937 he made a brilliant contribution to the foundations of the theory of probability. While in New York, Wald began to study the theory of statistics and, already in 1939, published one of his most important papers on the subject. Many other papers followed, quite a number of them written jointly with Wald's followers and students. This brilliant career was suddenly interrupted in the fall of 1950 when Wald, and his wife, perished in an airplane accident during a lecture tour in India. The statistical community in this country and abroad was deeply shocked and saddened. The present volume, which contains a collection of Wald's papers especially selected by a committee of the Institute of Mathematical Statistics, reflects the warm feelings of the statistical fraternity.

The achievements of Wald are many, and they are all brilliant. Because of the limitations imposed by the framework of the present review, only two major points can be mentioned. One of these consists in the rediscovery of a very fruitful idea conceived at the end of the 18th century by Laplace, then briefly developed by Gauss and then, largely, forgotten.

As is well known, the general problem of mathematical statistics is to develop methods of using the results of observations subject to chance in order to draw conclusions regarding the chance mechanism that produces the observations. Laplace noticed that, in applying any such method, the statistician is very much in the position of playing a game of chance: if the chance mechanism produces "favorable" values of the observable variables, his conclusions will be right: on the other hand, if the chance variation provides him with "unfavorable" values of whatever he observes, his conclusions will be wrong. How wrong his conclusions will be also depends on chance. The possibility of the statistician's choosing among many possible methods of drawing conclusions corresponds, in a sense, to the possibility of a gambler's having something to say about the rules of the game he is about to play. In these circumstances, Laplace imagined that, with every decision made by the statistician as a result of dealing with some observations, there is connected a "loss" and that the greater the statistician's error, the greater the loss. From here on, there was just one step to the formulation of the basic problem of choice among the possible statistical procedures: select the one that minimizes the expected loss resulting from wrong judgments. Gauss' method of least squares is based on this same principle, except that Gauss' loss function is defined to be proportional to the square of the error committed. Curiously, while the method and, particularly, the machinery of least squares are generally remembered and widely used, the principle on which this method is based—that is, the idea of the loss function—was largely forgotten. Wald's work brought it back, and now it is being broadly developed. The novel developments are concerned with methods of drawing decisions which, in a sense, are optimum not for any particular loss functions, such as those contemplated by Laplace or Gauss, but for broadly defined classes of loss functions.

The second major achievement of Wald consists in the integration of the theory of statistics (theory of decisions based on observations subject to chance variation) with the theory of experimentation, to form what may be called the theory of experimental strategy. The honor of having initiated the theory of experimentation belongs to another outstanding contemporary statistician, R. A. Fisher. However, much as science owes Fisher, particularly for his ideas of randomization, the problems of experimentation considered by Fisher are concerned with the design of isolated experiments and may be termed the tactics of experimental work. Contrary to this, Wald's theory deals not with single experiments but with their totality in a given domain of study. In addition, using his ideas about sequential procedures, combined with the idea of the loss function for faulty judgments, Wald laid the foundations of an all-enveloping, unified theory of experimentation and statistical decision-making. This unified theory contemplates the possible cessation of experiments at each step and the adoption of a terminal decision regarding "the state of the universe" or continuation of experimentation with a novel setup.

These general ideas, combined with many brilliant particular developments, are reflected in *Selected Papers in Statistics and Probability by Abraham Wald*. It must have an honored place on the shelf of every scientific library and on the desks of most serious research workers.

J. Neyman
University of California, Berkeley

The Water Relations of Terrestrial Arthropods. Cambridge Monographs in Experimental Biology, No. 5. E. B. Edney. Cambridge University Press, New York, 1957. 109 pp. Illus. $3.

The special difficulties encountered by terrestrial arthropods, because of their small size, in obtaining and keeping a sufficient supply of water have attracted the attention of many workers during the past quarter-century. In this small volume, E. B. Edney, who was, until 1955, reader in entomology at the University of Birmingham and who is now professor of zoology at the University College of Rhodesia and Nyasaland, reviews critically the literature in this extremely active field. The book will be of particular interest to insect physiologists, but comparative physiologists, ecologists, and biologists in general will welcome it. There are nearly 250 refer-

ences and, of these, more than 200 were published in the period 1930–55.

The subjects covered in the six chapters include transpiration and cuticle structure, excretion and osmoregulation, gain of water, and water and body temperature. Despite the limitation suggested by the title, material on aquatic insects is also discussed. Edney's treatment of these subjects is concise and clear, and his criticisms of methods and conclusions—including some of his own—are illuminating. Transpiration, for example, has turned out to be a far more complex process than it was, until recently, believed to be. The many questions which Edney raises should stimulate new and better work in the field.

A search for factual errors in those aspects of the subject with which the reviewer is personally familiar has yielded only one sentence which might be questioned. On page 71 it is stated, "The evidence so far considered shows that in most eggs which absorb water this is restricted to a given period of development—it may be before diapause as in *Melanoplus,* or after, as in *Austroicetes.*" This statement holds for *Melanoplus bivittatus,* as Salt's work has shown, but is not true for *Melanoplus differentialis,* where water is taken up by the eggs both before and after diapause. The fact that two species of the same genus of grasshoppers behave so differently in this respect illustrates both the variety which may be encountered in closely related organisms and the risk of making generalizations even for a genus. Since there are more than 150 species of *Melanoplus* in North America, a considerable number of surprises, no doubt, still await those who investigate the water relations of their eggs.

Edney's compact and well-organized volume is a valuable addition to the series of monographs presently being published by the Cambridge University Press. All who are concerned with the important part played by water in biological processes will be interested in this book.

ELEANOR H. SLIFER
State University of Iowa

Nonparametric Statistics for the Behavioral Sciences. Sidney Siegel. McGraw-Hill, New York, 1956. 312 pp. $6.50.

Prior to the publication of *Nonparametric Statistics for the Behavioral Sciences,* isolated descriptions of nonparametric statistical tests and the necessary accompanying tables were inconveniently scattered throughout a highly varied literature. Sidney Siegel has performed a great service for behavioral scientists by cataloging, in a single volume, most of the available nonparametric procedures, along with tables of critical values. As a reference work, this book is not only convenient but almost indispensable. As an elementary textbook, it combines simplicity and systematic organization with many instructive illustrations, but there is, intentionally, very little presentation of the rationale and derivation of the techniques.

The book is organized around experimental designs; this makes it possible for a research worker to locate an appropriate procedure without knowing the associated significance tests by name. Each technique is described in terms of function, method, and, when relevant information is available, power and power-efficiency. Examples of each method follow a uniform format: null hypothesis, statistical test, significance level, sampling distribution, rejection region, and decision. Instead of producing annoying redundancies, this consistent treatment serves to clarify distinctive properties of the various tests and tends to pinpoint the differential advantages of alternative procedures.

The book also contains a section on measurement, in which the author takes a firm but polemical stand on scaling requirements. He makes a puristic but somewhat overstated case for the widespread application of nonparametric statistics by dismissing interval scales as rare phenomena in the behavioral sciences and then forbidding, for ordinal data, the operations of arithmetic necessary for computing means and standard deviations. However, even though ordinal scales are not completely isomorphic with the real number system, they do reflect certain numerical characteristics, and the sum of a random sample of ordinal numbers possesses statistical properties upon which significance tests may be based. Interpretations of arithmetic operations performed upon noninterval scales are by no means trivial, as pointed out by Lord in his discussion of nominal numbers and Chebyshëv's inequality [F. M. Lord, *Am. Psychologist* **8**, 750 (1953)].

Most nonparametric tests require only ranking information, and some are applicable even to nominal classes. One strong justification that is offered for their use in the social sciences is the difficulty experienced in meeting, for behavioral data, the interval scaling requirements attributed to parametric statistics. However, this issue is complicated by the problem of dimensionality in measurement, which is not mentioned in the present volume. Some of the nonparametric techniques that require ordinal data are illustrated with the California F Scale of Authoritarianism, which is a set of heterogeneous, multidimensional attitude statements. In a multidimensional domain such as authoritarianism, even unique ordinal properties are questionable, and, unfortunately, practical solutions for dimensionality are available only for interval numbers. However, nonparametric statistics are also recommended because of their distribution-free character, ease of computation, and the generality that is obtained by not making numerous and stringent assumptions about parameters. Because of these important properties, nonparametric techniques are widely applicable, and the present volume constitutes an excellent, nontechnical handbook for their use.

SAMUEL MESSICK
Educational Testing Service
and *Princeton University*

Advances in Cancer Research. vol. 4. Jesse P. Greenstein and Alexander Haddow, Eds. Academic Press, New York, 1956. 416 pp. Illus. $10.

The fourth volume of *Advances in Cancer Research* continues to maintain the high scholarship, completeness, and critical evaluation of the preceding reviews. Three of the eight papers deal with chemotherapy. The first chapter, by Sidney Farber and his associates, on "Advances in chemotherapy of cancer in man," is a remarkably up-to-date analysis which, with Stock's review in volume 2, forms a rather complete summary of the whole of this active area of current research on cancer. Galton's presentation, on "The use of myleran and similar agents in chronic leukemias," not only meets the requirements of the title but contains a discussion of clinical assessment, by a mature investigator, that is worthy of consideration by the younger clinicians now entering this field. Goldin, in a review entitled "The employment of methods of inhibition analysis in the normal and tumor-bearing mammalian organism," effectively demonstrates the valuable additional data that can be derived from carefully designed dose-response laboratory studies in which the drug, the host, and the tumor are considered as an interrelated system.

The very selective review on "Some recent work on tumor immunity," by Gorer, is a reflection of the revival of interest in this approach to cancer. The author is very helpful in orienting the reader to the relevant aspects of modern immunology, but this specialty has acquired a language of its own which will be a source of ever-increasing despair to the general biologist.

Grobstein's consideration of "Inductive tissue interaction in development" is an engrossing account of the recent

work on differentiation. The author is to be congratulated on limiting his mention of cancer to some two dozen lines and then proceeding to his topic without straining analogies.

Haven and Bloor attempt to present much of the available information on "Lipids in cancer"—a rich diet in which more evaluative predigestion would have been useful. The most intriguing work reported is that on the beneficial effects of including tumor tissue (now further localized to the phospholipid portion of such tissue) in the diet of rats that bear tumors.

Under the title "The relation between carcinogenic activity and the physical and chemical properties of angular benzacridines," Lacassagne and his group make available, in English, their complex theoretical analysis of the *K* region in the molecular structure of carcinogens. The search for biochemorphologic features at the electron level is undoubtedly worth while but, alas, beyond my capacities to review.

Mühlbock, in the last paper, on "The hormonal genesis of mammary cancer," presents this old topic in a somewhat different and informative fashion. Of particular interest is the attempted and reasonable reconciliation of the hormonal aspects of mammary tumors in mice and in the human female.

The editors, Jesse P. Greenstein and Alexander Haddow, and the publisher are to be congratulated for their valuable contributions to the cancer literature. The value of the reviews would be increased by including the titles of the references. If these were numbered and referred to by number in the text, most of the additional space would be compensated for, and the distraction of having too many parenthetical names and dates in the text would be obviated.

MICHAEL B. SHIMKIN
National Cancer Institute,
National Institutes of Health

Separation and Purification. vol. III, pt. 1, of *Technique of Organic Chemistry.* Arnold Weissberger, Ed. Interscience, New York, ed. 2, 1956. 873 pp. Illus. $17.50.

The former volume III in this admirable series possessed no title and treated of a diverse group of topics. In the present revision, the volume has been divided into two parts: part I, *Separation and Purification,* reviewed here, and part II, *Laboratory Engineering,* to be reviewed later. Into the latter portion have gone those topics that are concerned primarily with reactants and the reaction itself: "Selection of materials for the construction of equipment" (new); "Heating and cooling" (revised); "Grinding, screening, and classifying" (new); "Mixing" (little changed); and "Operations with gases" (new). It may be added parenthetically that it is the "laboratory" aspects of the subject which are stressed, rather than the "engineering" approach.

Into part I have gone those topics that are concerned with the isolation, separation, purification, and identification of mixtures of products and of other compounds. Most of the sections of part I have been revised, and expanded also, so that, while the former single volume contained only 671 pages, the two parts now total 1284 pages. It seems significant that each chapter has been expanded, if only by four pages, so that the reader may well ask why the authors invariably add newer material to the older rather than allowing natural selection to replace the outmoded by the modern.

The chapter headings of part I are as follows: "Diffusion methods," including "Thermal diffusion of organic liquids" (new), "Barrier separations" (new), "Dialysis and electrodialysis" (little changed), and "Zone electrophoresis" (new); "Laboratory extraction and countercurrent distribution" (revised), including a section on "Liquid-liquid extraction for increased quantities" (new); "Crystallization and recrystallization" (revised); "Centrifuging" (revised); "Filtration" (revised); and "Solvent removal, evaporation and drying" (revised).

The major revisions in the present volume, when compared with the corresponding portion of the previous edition, reflect rather accurately the areas of greatest recent activity. This is particularly apparent in the first chapter, which contains three completely new sections, not found in the earlier edition. The techniques of thermal diffusion, barrier separations (molecular sieves), and zone (paper) electrophoresis have become prominent only in very recent years, and a majority of the references in these three sections are to the literature since 1950, the date of the previous edition of this work.

In the chapters that have been revised from the first edition, the more active areas also have been greatly enlarged. Thus, R. S. Tipson's "Crystallization and recrystallization" now contains an excellent 15-page treatment of molecular compounds and inclusion complexes, while D. and L. C. Craigs' "Laboratory extraction and countercurrent distribution" devotes 20 pages to their highly successful automatic countercurrent distribution apparatus and 12 pages (with seven tables) to the selection of suitable solvent systems. A similar welcome expansion has been accorded the section on freeze-drying in the late Geoffrey Broughton's "Solvent removal . . ." chapter.

There are, of course, omissions. I would have welcomed a discussion of the commercially available zeolite molecular sieves in the "Barrier separation" section, a treatment of three-phase countercurrent distribution in the extraction chapter, and an application of freeze-drying techniques to nonaqueous systems. For those who are unfamiliar with the "Technique of organic chemistry" series, it may be worth while to note that additional separation and isolation techniques are treated in other volumes; for example, "Distillation" (vol. IV), "Adsorption and chromatography" (vol. V), "The ultracentrifuge" (vol. I, part I), and "Electrophoresis" (vol. I, part II).

However, the observations which are applicable to the series in general may, with conviction, be applied to the present volume. It is well written, it is profusely illustrated, and it is thorough in its treatment, maintaining a nice balance of theoretical and practical aspects. It must indeed rank as a standard reference work.

KENNETH L. RINEHART, JR.
University of Illinois

High Energy Accelerators. vol. 1 of *CERN Symposium on High Energy Accelerators and Pion Physics, Proceedings.* Geneva, 11–23 June 1956. European Organization for Nuclear Research, Geneva, 1956. 567 pp. Illus. F. 40.

This book is the first volume of a two-volume report on the European Organization for Nuclear Research (CERN) Symposium. It covers the material presented in the first week of the symposium.

After an introduction by J. B. Adams of CERN, the first section concerns new ideas for high-energy accelerators. In this section are papers concerning fixed-frequency alternating-gradient accelerators, fixed-frequency cyclotrons, and ideas about colliding beam accelerators. Here, also, are some Russian ideas about completely new possible methods for acceleration of particles, with the aid of plasmas, and so forth.

The second section is about problems connected with the transition energy in alternating-gradient accelerators. Here again, the Russian workers have a novel idea for circumventing this problem.

The third session has to do with the problems of getting particles out of machines. In this section there are papers concerning some of the existing synchrotrons and synchrocyclotrons as well as proposals for new machines. The following seven sections cover, in turn, linear accelerators and injection problems, non-

linear betatron oscillations, magnet problems (here, the Russians report on their 680-Mev synchrocyclotron and also on their new 10-Bev synchrotron, which is about complete), radio-frequency acceleration, electron-synchrotron problems, problems in the use of accelerators (this section covers only experience with existing machines), and, finally, general topics, including the Princeton-Pennsylvania proton-synchrotron and the Stanford linear accelerator.

This book is well printed. There are numerous errors, which arise from the difficulty of getting authors who are scattered all over the world to check their contributions carefully and quickly. In general, these do not cause trouble in reading. A more serious criticism is that, since the meeting was attended mainly by experts, many of the papers will be found to be very difficult to follow by anyone not familiar with the subject. However, the book does contain a great deal of information on the new types of accelerators, most of which is not published elsewhere except in the internal reports of the groups working on these problems. It is, therefore, a very valuable book for anyone who wishes to become a specialist, and many parts of it will be found useful by anyone desiring information about these new ideas.

ROBERT O. HAXBY
Midwestern Universities Research Association

Early Electrical Machines. The experiments and apparatus of two enquiring centuries (1600 to 1800) that led to the triumphs of the electrical age. Bern Dibner. Burndy Library, Norwalk, Conn., 1957. 57 pp. Illus. $1.50.

The picture of Otto von Guericke pursuing a drifting feather with his rubbed sulfur globe not only recalls a landmark in the history of electricity but constitutes a fit symbol of the instrument through the use of which, in the course of a century and a half, a miscellany of occult manifestations of nature were assembled into a science. Bern Dibner has undertaken to write a commemoration of that instrument, which is at the same time an excellent capsule history of electricity during the heyday of the electric machine.

Histories of electricity tend to become bloodless when the illustrations and descriptions of the quaint experiments—as they seem to us—are eliminated. A book such as this, which dwells on this era, rather than hurrying through it and touching only the "high spots," is an interesting and useful antidote to the malady of oversimplification which often afflicts works on the history of science. The illustrations in the present work are well selected and beautifully reproduced, and Dibner has given a fuller than usual account of the multitudinous experiments of the empirically minded electricians of the 17th and 18th centuries.

Modern technologists, it is to be feared, give too little thought to the debt owed their predecessors. It is pleasant to know of an outstanding exception in Dibner, whose beautiful and well-written publications on the history of science have gained him a well-deserved reputation, both as a student and as a patron of the history of science and technology.

ROBERT P. MULTHAUF
Smithsonian Institution

Ernest Rutherford, Atom Pioneer. John Rowland. Philosophical Library, New York, 1957. 160 pp. $4.75.

Ernest Rutherford was born on 30 August 1871, near the town of Nelson, New Zealand, and died on 19 October 1937 in Cambridge, England. Into this all too short life of 66 years (his father and mother lived to the age of 89 and 92 years, respectively) there were crowded an incredible number of scientific accomplishments and honors. At the age of 23 he earned his B.Sc. degree in New Zealand and left for the Cavendish Laboratory, Cambridge, with the aid of the single available scholarship. Three years later he earned a B.A. research degree and 1 year thereafter, at the age of only 27, he became Macdonald professor of physics at McGill University, Montreal, Canada. Nine years later he took charge of the physics department at Manchester University, England, and after another 12 years, at the age of 48, he succeeded his old teacher, J. J. Thomson, in England's most distinguished position in physics, that of Cavendish professor at Cambridge, a position he held until his death.

At McGill, Rutherford laid the experimental foundations of the entire field of radioactivity and wrote the first and second editions of his authoritative book of that title. At Manchester his theory of the nuclear atom was born and experimentally established. At Cambridge, in 1919, he accomplished, for the first time, the artificial transmutation of elements, using alpha-ray bombardment to transform ordinary nitrogen into an isotope of oxygen.

In 1903, at the age of 32, Rutherford became a fellow of the Royal Society (and in 1925, its president); at the age of 37 he received the Nobel prize, *in chemistry;* at the age of 43 he was knighted, and at the age of 60, he became a baron.

Rutherford was an experimental genius, with comparatively little facility in mathematics and with slight sympathy for involved mathematical theories. In this he was much like Faraday, in whose papers, as Rutherford once pointed out, there does not appear a single line of mathematics. When Rutherford was asked, in 1929, to address the British Association, meeting in South Africa, on "The trend in modern physics," he replied that such a topic would not take more than 2 minutes to deal with. "All I could say would be that the theoretical physicists have got their tails up, and it is time that we experimentalists pulled them down again!"

Until close to the time of his death, Rutherford enjoyed the most robust health. He was often taken, by strangers, for a farmer rather than a professor. He married a childhood sweetheart (after an engagement of 5 years!) and had an exceptionally peaceful and happy married life. In spite of the honors heaped upon him, Rutherford preserved to the end his innate modesty. He was always generous in his recognition of the work of others, including that of his coworkers. He was a tremendously hard worker and expected the same of his assistants. But he was both respected and loved by everyone who had associations with him. An intimate friend said of him, "Rutherford never made an enemy and never lost a friend." There are truly few persons in all scientific history who can so well be chosen as a model and an inspiration to others in the field. For just this reason it is appropriate that the details of Rutherford's scientific and personal life be widely publicized.

Such details are, in fact, contained in his official biography, written only 2 years after his death by A. S. Eve, a distinguished physicist and a close friend and colleague of Rutherford at McGill University. Eve's book is very interesting as well as authoritative. Now John Rowland has written a much more condensed biography. The major portion of Eve's material consists of letters to and from Rutherford, both personal and scientific. Nearly 300 such letters are quoted in full or in part, and they constitute collectively the most intriguing feature of the volume for the professional scientist.

Rowland's new book, on the contrary, merely quotes a sentence here and there from such letters. It represents, however, a well-selected and well-written brief account of Rutherford's life and can be read with profit and pleasure by a large section of the public. Unfortunately it closes with an eleven-page "Epilogue" on advances in physics since the death of Rutherford. Here Rowland falls down badly. For instance, Fermi, in place of McMillan, is credited with the discovery of the first transuranium element, neptunium. Rowland's description of the re-

actions that occur in the hydrogen bomb is quite incorrect. He makes no distinction between the process of fission (A-bomb) and that of fusion (H-bomb) and there is, in fact, no indication that he even realizes that there is a difference.

The other feature of Rowland's book that disturbs me is the price. Eve's book is handsomely bound, printed on 451 large pages of high-grade paper, with 17 plates of photographs, plus the frontispiece, and six line drawings. Rowland's book, which contains not more than one-fourth as many words, is printed on 160 small pages of ordinary paper, with three line drawings and no photographs, except for the frontispiece. Yet Eve's book sold in 1939, and still does sell, for $5, whereas Rowland's book sells at $4.75—surely a glaring example of the effects of inflation, if nothing more. But it is an interesting and reliably written book, provided that the reader overlooks those last 11 misleading pages.

RAYMOND T. BIRGE
University of California

Progress in the Chemistry of Organic Natural Products. vol. 13. L. Zechmeister, Ed. Springer, Vienna, 1956. 624 pp. Illus. $25.60.

The timely coverage of important developments in the field of natural products has been maintained in this 13th volume of the Zechmeister series. The various topics are discussed with competence and clarity by the foremost research workers in the field, and a multitude of formulas, conveying structures and reaction schemes, are presented.

The first chapter, by A. R. H Cole, deals with the application of infrared spectroscopy to the elucidation of the structure of natural products, with primary emphasis on steroids and terpenoids. A short discussion is also devoted to the polyenes. The description of the various instruments and sampling techniques could well have been omitted, since they have been considered in various other books.

O. T. Schmidt discusses the progress of the chemistry of tannins since 1929 in the second chapter. The third chapter, by C. Tamm, deals with the progress of research in the field of cardioactive glycosides. The isolation and properties of the various glycosides are described. In the discussion of structure determinations, degradation reactions and structures of aglycones are emphasized.

The recognition of the importance of naturally occurring tropolones and troponoids is well treated in the fourth chapter, by T. Nozoe. A description of structure determination of natural tropolones is given, and general methods for the synthesis of various types of tropolones are outlined.

Alkaloids that are related to anthranilic acids are reviewed by J. R. Price in the fifth chapter. Quinoline, acridine, furoquinoline, quinazoline, and quindoline alkaloids are included here.

The final two chapters, by A. Chatterjee, with S. C. Pakrashi and G. Werner, and by W. Grassman, with E. Wünch, deal, respectively, with recent developments in the chemistry and pharmacology of *Rauwolfia* alkaloids and with the syntheses of peptides.

HENRY FEUER
Purdue University

New Books

The Exploration of the Colorado River. John Wesley Powell. University of Chicago Press, Chicago, Ill., 1957 (abridged from ed. 1, 1875). 159 pp. $3.75.

The Chemistry of Plants. Erston V. Miller. Reinhold, New York; Chapman & Hall, London, 1957. 181 pp. $4.75.

Physiology of the Nervous System. E. Geoffrey Walsh. With chapters on somatic sensibility and the applied physiology of pain by John Marshall. Longmans, Green, New York, 1957. 579 pp. 50s.

Précis de Biologie Humaine. Les bases organiques du comportement et de la pensée. Propédeutique biologique des étudiants en psychologie et sciences humaines. Paul Chauchard. Presses Universitaires de France, Paris, 1957. 415 pp. Paper, F. 1400.

Précis de Biologie Animale. M. Aron and P. Grassé. Masson, Paris, 1957. 1421 pp. Cloth, 1 vol., F. 5900; paper, 2 vol., F. 5300.

Physics. Erich Hausmann and Edgar P. Slack. Van Nostrand, Princeton, N.J., ed. 4, 1957. 732 pp. $8.

A Monograph of the Immature Stages of African Timber Beetles. E. A. J. Duffy. British Museum (Natural History), London, 1957. 345 pp. £5.5s.

Heat Transfer and Fluid Mechanics Institute, 1957. Preprints of papers. Held at California Institute of Technology, Pasadena, 19–21 June. Stanford University Press, Stanford, Calif., 1957. 446 pp. $8.50.

Evolution of the Veterinary Art. A narrative account to 1850. J. F. Smithcors. Veterinary Medicine Publishing Co., Kansas City, Mo., 1957. 417 pp.

Seminar on the Decline of Materialism. Sponsored by the Laymen's Movement for a Christian world, 10–11 Nov. 1956, Wainwright House, Milton Point, Rye, N.Y. Laymen's Movement for a Christian World, 347 Madison Ave., New York 17, 1957. 108 pp.

Medical Department, United States Army, Surgery in World War II. Orthopedic Surgery in the Mediterranean Theater of Operations. John B. Coates, Jr., Ed.-in-Chief. Office of the Surgeon General, Department of the Army, Washington, D.C., 1957 (order from Supt. of Documents, GPO, Washington 25). 388 pp. $4.

Miscellaneous Publications

(Inquiries concerning these publications should be addressed, not to Science, but to the publisher or agency sponsoring the publication.)

West African Maize Research Unit, Second Annual Report. 1954. West African Research Unit, Moor Plantation, Ibadan, Nigeria, 1957. 51 pp. 5s.

Study Group on the Ecology of Intermediate Snail Hosts of Bilharziasis, Report. WHO Tech. Rept. Series No. 120. 38 pp. $0.30. *Study Group on Atherosclerosis and Ischaemic Heart Disease, Report.* WHO Tech. Rept. Series No. 117. 40 pp. $0.30. *The Work of WHO, 1956.* Official records of the World Health Organization, No. 75. Annual report of the Director-General to the World Health Assembly and to the United Nations. 233 pp. $2. World Health Organization, Geneva, 1957.

Home Study Blue Book. Homer Kempfer, Ed. National Home Study Council, Washington, ed. 19, 1957. 32 pp.

Energy Transfer in Polyacene Solid Solutions. A guide to the literature to the end of 1956. NRC No. 4320. F. R. Lipsett. Radio and Electrical Engineering Div., National Research Council of Canada, Ottawa, 1957. 64 pp. $0.50.

A Spectacular Waterfowl Migration through Central North America. Biological Notes No. 36. Frank C. Bellrose. State Natural History Survey Div., Urbana, Ill., 1957. 23 pp.

Individual Differences in Night-Vision Efficiency. Medical Research Council Special Report Series No. 294. M. H. Pirenne, F. H. C. Marriott and E. F. O'Doherty (with a section on *The Frequency of Seeing at Low Illumination* by H. K. Hartline and P. R. McDonald). Her Majesty's Stationery Office, London, 1957. 83 pp. 8s.

Stress; Experimental Psychology; Child Psychiatry. Psychiatric Research Reports, 7. Jacques S. Gottlieb, Chairman, Editorial Committee. American Psychiatric Assoc., Washington 6, 1957. 88 pp. $2.

The Nature and Transmission of the Genetic and Cultural Characteristics of Human Populations. Papers presented at the 1956 annual conference of the Milbank Memorial Fund. Milbank Memorial Fund, New York, 1957. 143 pp. $1.

Abstracts of Research Financed by the Petroleum Research Fund, 1954–1956. Administered by the American Chemical Society. Petroleum Research Fund, Washington, 1957 (order from Secretary, Petroleum Research Fund Advisory Board, 1155 16 St., NW, Washington 6). 34 pp.

Proceedings of the Symposium on Rauwolfia. Held under the auspices of the Pharmaceuticals and Drugs Committee of the Council of Scientific and Industrial Research on 17–19 October 1955 at the All-India Institute of Hygiene and Public Health, Calcutta. Reprinted from *The Indian Journal of Pharmacy*, vol. XVIII, Nos. 4–7, 1956. Popular Press, Bombay, 1957. 148 pp.

Symposium on Techniques in Polymer Science. With an introduction by C. H. Bamford. Lectures, Monograph and Reports, 1956, No. 5. Royal Institute of Chemistry, London, 1957. 79 pp. $1.15.

Meetings and Societies

Mathematics Instruction

The second AAAS Conference on Mathematics Instruction was held in Washington in the AAAS board room, 13–14 May 1957. At the meeting of the Policy Committee for Mathematics that was held in Rochester, N.Y., in December 1956, the secretary of the committee, who had attended the first conference, reported that a great deal of useful information had been presented but that there had been insufficient time to formulate concrete plans for the needed further consideration of these various studies. Subsequently, at the request of the policy committee, the AAAS called the second conference, which was made possible by a grant from the Carnegie Corporation of New York. There were 24 participants, most of whom had attended the first conference as well. The presiding chairman was Dean W. L. Duren, Jr., of the University of Virginia.

The conference approved 19 motions, in the form of recommendations or resolutions. While all of the motions are of general interest to scientists, resolutions 1, 2, and 3 are addressed particularly to the departments of education of the states; 4, 5, and 6, to mathematicians; 7, 8, and 9, to the Policy Committee for Mathematics; 10, to the Mathematical Association of America (MAA); 11 and 12, to the National Council of Teachers of Mathematics (NCTM); 13 and 14, to the American Association for the Advancement of Science (AAAS); and the remainder, to the National Science Foundation (NSF). The resolutions and recommendations of the conference are as follows:

1) That this Conference call the attention of school authorities on state and local levels to the facts that there is at present widespread interest in the improvement of mathematical instruction and that there are significant programs of discussion, activity, and experimentation in the area of curricular revision in mathematics presently in progress; and that the Conference recommend that these interests and activities be recognized by the appointment of committees or study groups on the state and local levels to consider problems of curricular revision, and especially to familiarize themselves and their constituents with the studies of significant programs, and to determine the applicability to the state or local situations of the findings and recommendations of these groups.

2) That this Conference recommend that states provide supervisory service for elementary and secondary mathematical programs by a person or persons of recognized competence in mathematics.

3) That this Conference request that the Director of the Science Teaching Improvement Program send resolutions 1 and 2 to state superintendents of education and also further publicize them in appropriate journals.

4) That this Conference recommend to college and university departments of mathematics that they offer courses planned for prospective and in-service elementary teachers, and that departments of mathematics seek the cooperation of the education departments of their colleges, to the end that such courses be required of elementary teachers.

5) In view of the current interest in the improvement of mathematics curriculums and the importance to this country of improved mathematical training in the schools, that this Conference urge that more mathematicians devote a fraction of their time, when so requested, to meeting with and assisting teachers who are planning and putting into effect such improved courses.

6) That this Conference call attention to the need for additional study, involving mathematicians, of mathematics programs grades 1 to 8.

7) That this Conference recommend that the Policy Committee for Mathematics consider the question of minimum certification requirements for teachers of mathematics.

8) That this Conference recommend that the Policy Committee for Mathematics prepare and distribute, in large numbers, two 1- or 2-page leaflets, one on careers in teaching mathematics and one on other careers in mathematics.

9) That this Conference refer to the Policy Committee for Mathematics the question of support for legislation to build mathematics buildings in colleges and universities.

10) That this Conference recommend to the MAA that it take steps, in cooperation with NCTM, to extend the visiting lecturer program to high schools.

11) That this Conference refer to NCTM the question of preparing a guide for curriculum studies in mathematics, for the use of city and county school systems and state groups. The guide would point out ways in which curriculums in mathematics can be developed to meet current needs and take advantage of the national interest in the improvement of mathematics instruction at all levels.

12) That this Conference endorse the curriculum study of the NCTM.

13) Whereas significant efforts have been made to recruit students for such professions as engineering and to enroll [them] in courses in sciences and mathematics, and whereas such efforts have greatly increased the demand for instruction in mathematics, and whereas no comparable efforts have been made to recruit an adequate supply of qualified teachers of mathematics to offer such instruction, be it resolved that this Conference urge that the Science Teaching Improvement Program of the AAAS continue to undertake to secure funds and direction for a program to encourage students in junior and senior high schools and in colleges to enter the profession of the teaching of mathematics.

14) That this Conference recommend that AAAS sponsor a conference in which the mathematical organizations would meet with scientists and engineers to learn what mathematics courses would best support new science.

15) That this Conference recommend to NSF that the Science Faculty Fellowship Program be extended to the high-school level.

16) That this Conference recommend to the NSF that there be more summer institutes programmed for junior high school teachers; and that it publicize this recommendation among colleges which might hold such institutes.

17) That this Conference recommend that NSF consider follow-up of some summer institutes by consulting service; and that it instruct such institutes to try, when possible, to include two or more teachers from the same school system.

18) That this Conference go on record in favor of increasing the number of summer institutes for college teachers of mathematics.

19) That this Conference recommend that NSF consider experimental institutes in mathematics for elementary teachers.

JOHN R. MAYOR
American Association for the Advancement of Science

Antibiotics

The fifth annual Symposium on Antibiotics will be held 2–4 Oct. at the Willard Hotel, Washington, D.C. It is sponsored by the Division of Antibiotics of the Food and Drug Administration, U.S. Department of Health, Education, and Welfare, with the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy*.

There is no registration fee. Abstracts of no more than 200 words (five copies) must be submitted *no later than 19 Aug.* The abstract should explain briefly not only what was done in the study but the results obtained. The original manuscript and one copy must be submitted *by 2 Sept.* to Dr. Henry Welch, Division of Antibiotics, Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Washington 25, D.C.

Nuclear Structure

An International Conference on Nuclear Structure devoted to the experimental and theoretical aspects of low-energy phenomena will take place at the Weizmann Institute of Science, Rehovoth, Israel, from 9 to 13 Sept., under the auspices of UNESCO and the International Union of Pure and Applied Physics. Sessions will consist of two or three lectures, followed by a 45-minute discussion. Those who expect to take part in the discussions have been requested to submit a résumé of their comments in advance. About 150 scientists from 15 different countries are expected to participate.

A 3-day tour of the country from 14 to 16 Sept. will follow the conclusion of the sessions. Inquiries may be addressed to the secretary of the conference, A. de-Shalit, Weizmann Institute, Rehovoth, Israel.

Geodesy and Geophysics

More than 1500 specialists in the earth sciences will gather in Toronto 3–14 Sept. to hold the 11th general assembly of the International Union of Geodesy and Geophysics. The main topic will be the International Geophysical Year (IGY). Delegates from 50 countries in all parts of the world will review the IGY opening and lay final plans for the vast joint enterprise.

The meeting in Toronto will bring together IUGG's seven international associations, whose interests cover nearly all aspects of the IGY. J. T. Wilson, head of the Geophysics Laboratory of the University of Toronto, is in charge of arrangements. He is also vice-president of the IUGG.

International Scientific Radio Union

Sixteen countries, exclusive of the United States, have already appointed a total of 141 delegates to attend the 12th general assembly of the International Scientific Radio Union, which will meet 22 Aug. to 5 Sept. in Boulder, Colo. Nine other countries, including the U.S.S.R., are still expected to name delegates. The number of U.S. delegates appointed so far totals 139. This closed meeting of radio scientists will be limited to approximately 500 delegates and observers.

Invited to the United States by the U.S. national committee of the union, the scientists will have as local hosts the Boulder Laboratories of the National Bureau of Standards, the University of Colorado, the High Altitude Observatory, and the city of Boulder. Kenneth A. Norton, chief of the NBS radio propagation engineering division, is chairman of local arrangements.

This cooperation in basic research is brought about largely through the efforts of the permanent International Scientific Radio Union commissions that conduct continuous studies in the major fields of radio research. The assemblies, which are held every 3 years with one of the member countries serving as host, allow representatives of the commissions to pool information on present radio studies and to outline over-all plans for future international research programs. This will be the first time since 1927 that the United States has been host to the assembly.

Society Organized for Biophysicists

The Biophysical Society was organized early this year to encourage biophysical research in three ways: by increasing communication among the highly diversified scientists working in this field, by furthering the training of biophysicists and by promoting the application of research techniques from physics to biological problems. More than 500 scientists from 200 institutions throughout the United States met in Columbus, Ohio, to discuss the problems, purposes, and desirability of founding a society that would protect and promote the interests of biophysicists. The society will attempt to define further the biophysical field and draw into it the engineering, medical, biological, and physics talent that should serve it.

Elected to lead the new society as chairman was Robley C. Williams of the University of California, Berkeley; Otto H. Schmitt, of the University of Minnesota, vice chairman; Ralph W. Stacy of Ohio State University, treasurer; and Samuel A. Talbot of Johns Hopkins School of Medicine, secretary. A 20-man council also was named. Its members, in addition to the officers, include: E. C. Pollard, W. A. Rosenblith, F. D. Carlson, K. S. Cole, H. K. Hartline, M. A. Lauffer, C. Levinthal, E. Rabinowitch, N. R. Rashevsky, A. Rich, R. B. Roberts, F. O. Schmitt, A. K. Solomon, H. B. Steinbach, C. A. Tobias, and R. E. Zirkle.

Forthcoming Events

September

9–11. Electron Microscope Soc. of America, annual, Cambridge, Mass. (D. M. Teague, Chrysler Corp., Box 1118, Detroit 31, Mich.)

9–11. Quantitative Methods of Mammalian Cell Culture, 2nd annual, Denver, Colo. (Office of Graduate and Postgraduate Education, Univ. of Colorado Medical Center, Denver 20.)

9–13. Illuminating Engineering Soc., annual, Atlanta, Ga. (A. D. Hinckley, IES, 1860 Broadway, New York 23.)

9–13. Instrument Automation Conf., 12th annual, Cleveland, Ohio. (Instrument Soc. of America, 313 Sixth Ave., Pittsburgh, Pa.)

9–13. Neutron Interaction with Nuclei, internatl. conf. of IUPAP, New York. (W. W. Havens, Pupin Cyclotron Lab., Columbia Univ., 538 W. 120 St., New York 27.)

9–13. Society of Photographic Scientists and Engineers, annual, Asbury Park, N.J. (Society of Photographic Scientists and Engineers, Box 1609, Central Station, Washington, D.C.)

9–15. Macromolecular Chemistry, internatl. symp., IUPAC, Prague, Czechoslovakia. (Secretariat, ISMC, 5, Technická, Prague 6.)

9–20. Radio-Isotopes in Research, UNESCO conf., Paris, France. (UNESCO House, 19, avenue Kléber, Paris 16°.)

10–13. Alaskan Science Conf., 8th, Anchorage. (C. J. Beers, U.S. Coast and Geodetic Survey, College, Alaska.)

10–13. American Statistical Assoc., annual, Atlantic City, N.J. (D. C. Riley, ASA, 1757 K St., NW, Washington 6.)

10–13. Biometric Soc., Eastern North American region, Atlantic City, N.J. (A. M. Dutton, Box 287, Sta. 3, Rochester, N.Y.)

10–13. Econometric Soc., Atlantic City, N.J. (R. Ruggles, Dept. of Economics, Yale Univ., New Haven, Conn.)

10–13. Institute of Mathematical Statistics, annual, Atlantic City, N.J. (G. E. Nicholson, Jr., Dept. of Statistics, Univ. of North Carolina, Chapel Hill.)

14–15. Minnesota Acad. of Science, Cedar Creek Forest. (M. R. Boudrye, 51 University Ave., St. Paul 3, Minn.)

15–18. American Inst. of Chemical Engineers, natl., Baltimore, Md. (F. J. Van Antwerpen, AIChE, 25 W. 45 St., New York 36.)

16–21. Orthopedic Surgery and Traumatology, 7th internatl. cong., Barcelona, Spain. (J. M. Vilardell, Avenida Jose Antonio 654, Barcelona.)

17–20. International Union of Pure and

Applied Physics 9th general assembly, Rome, Italy. (P. Fleury, IUPAP, 3, boulevard Pasteur, Paris 15e, France.)

17–24. Industrial Chemistry, 30th internatl. cong., Athens, Greece. (Committee of Organization, 30th internatl. Cong. of Industrial Chemistry, Rue Kaningos 10, Athens.)

18–20. Formation and Stabilization of Free Radicals, symp., Washington, D.C. (A. M. Bass, Free Radicals Research Section, National Bureau of Standards, Washington 25.)

18–21. Child Psychology Symp., Worcester, Mass. (D. Evans, News Bureau, Clark Univ., Worcester.)

18–21. International Mineral Dressing Cong., Stockholm, Sweden. (J. Hedlund, IMDC, Näckströmsgatan 1III, Stockholm C.)

19–21. Office Dermatology, postgraduate conf., San Francisco, Calif. (Office of the Dean, Stanford Univ. School of Medicine, 2398 Sacramento St., San Francisco 15.)

22–28. Mesons and Recently Discovered Particles, colloquium, IUPAP, Venice, Italy. (A. Rostagni, Istituto di Fisica dell' Universita, Via Marzolo 8, Padua, Italy.)

23–24. Fluid Flow in Porous Media, Conf., Norman, Okla. (C. G. Dodd, Petroleum Engineering Dept., Univ. of Oklahoma, Norman.)

23–25. American Soc. of Mechanical Engineers, fall, Hartford, Conn. (C. E. Davies, ASME, 29 W 39 St., New York 18.)

23–27. International Soc. of Bioclimatology and Biometeorology, Vienna, Austria. (S. W. Tromp, Hofbrouckerlaan 54, Oegstgeest-Leiden, Holland.)

24–25. Industrial Electronics Conf., Chicago, Ill. (E. A. Roberts, Union Thermoelectric Corp., 2001 Greenleaf St., Evanston, Ill.)

25–27. Mississippi Valley Medical Soc., annual, St. Louis, Mo. (H. Swanberg, 510 Maine St., Quincy, Ill.)

28–30. American College of Hospital Administrators, 23rd annual, Atlantic City, N.J. (D. Conley, ACHA, 620 N. Michigan Ave., Chicago 11, Ill.)

29–5. World Medical Assoc., Istanbul, Turkey. (L. H. Bauer, 10 Columbus Circle, New York 19.)

30–2. American Oil Chemists' Soc., fall, Cincinnati, Ohio. (Miss L. R. Hawkins, AOCS, 35 E. Wacker Dr., Chicago 1, Ill.)

30–8. International Council for the Exploration of the Sea, 45th annual, Bergen, Norway. (A. Fridriksson, ICES, Charlottenlund Slot, Charlottenlund, Denmark.)

October

1–4. American Roentgen Ray Soc., annual, Washington, D.C. (B. R. Young, Germantown Hospital, Philadelphia 44, Pa.)

2–4. American Soc. of Photogrammetry, semi-annual, St. Louis, Mo. (C. E. Palmer, ASP, 1515 Massachusetts Ave., NW, Washington 5.)

2–4. Antibiotics, 5th annual symp., Washington, D.C. (H. Welch, Div. of Antibiotics, Food and Drug Administration, U.S. Dept. of Health, Education, and Welfare, Washington 25.)

(See issue of 19 July for comprehensive list)

EQUIPMENT NEWS

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Science *does not assume responsibility for the accuracy of the information. All inquiries concerning items listed should be addressed to* Science, *Room 740, 11 W. 42 St., New York 36, N.Y. Include the name(s) of the manufacturer(s) and the department number(s).*

■ ANALOG-TO-DIGITAL CONVERTER accepts electric signals in ranges from 1 mv to several volts full scale and converts them into angular displacement by means of a servomechanism. Angular displacement is then converted to digital code representation in the form of contact closures by interchangeable drums coded with contact pins arranged in up to 16 rows. Each row has 200 quantizing positions. (Union Thermoelectric Corp., Dept. S458)

■ PROGRAMED POWER SUPPLY supplies d-c voltages in 1-volt steps from −300 to +300 v and at currents from 0 to 200 ma. Programing is furnished by punched tape or by any system which supplies binary-coded decimal signals. Voltages are selected by applying pulses to a group of relays. These operate in conjunction with precision-made, wire-wound, voltage-dividing resistors. Response time is 200 msec. (Dressen-Barnes Corp., Dept. S471)

■ PULSE-HEIGHT ANALYZER is available in capacities from 10 to 50 channels in increments of 10 channels. A maximum of 99,999 counts may be accumulated in each channel at counting rates up to 15,000 count/min. Readout is accomplished by a scale-of-ten glow transfer tube followed by a four-digit register. Double-pulse resolution time is 4 μsec. Discriminator window width is fixed at 2.0 v, stable within ±1 percent. (El Dorado Electronics Co., Dept. S474)

■ PORTABLE OSCILLOSCOPE has a pass band from direct current to 10 Mcy/sec. Vertical amplification is variable from 0.01 to 50 v per division in 12 steps. The time base provides 22 calibrated steps from 0.2 μsec to 2 sec per division. A 3-in. cathode-ray tube with an accelerating potential of 1.85 kv is used. The power supply is electronically regulated. (Tektronix Inc., Dept. S488)

■ ULTRARAPID FLASHER provides flash repetition rates to 20,000/sec. Flash duration is of the order of 1 μsec. Energy per flash can be varied from 0.3 to 5 watt seconds. At flashing rates up to 1000/sec, continuous operation is possible. The light source is a demountable spark chamber. (Frank Fruengel Inc., Dept. S511)

■ PHOTOELECTRIC REFRACTOMETER compares the refractive index of a reference fluid to that of a process fluid. A self-nulling optical servo system provides a linear output signal suitable for actuation of recording and data-processing equipment. (Phoenix Precision Instrument Co., Dept. S480)

■ METAL DETECTOR has a maximum range of 7 feet for large objects. The instrument is battery operated, and the search coil is designed for underwater use. Proximity of metallic objects is indicated by meter deflection and by headphone sounds. (Gardiner Electronics Co., Dept. S499)

■ PULSE CALIBRATOR measures amplitude, duration, and rise time of current and voltage pulses. The instrument permits visual display of two signals. One of these, the signal to be measured, can be alternating current, direct current, or a pulse of either polarity. The other is a known reference voltage which is used as a measuring standard. The reference voltage is variable by means of a helical attenuator. Accuracy of calibrating voltage is ±0.1 percent. A mercury cell is used as the standard to set the reference voltage. (Burroughs Corp., Dept. S481)

■ DIGITAL VOLTMETER measures low-level voltages obtained from thermocouples, strain gages and other transducers. The instrument uses stepping switches, operating in oil, to effect balance. Range is ±0.001 to ±9.999 mv with sensitivity of 3 to 5 μv and accuracy ±0.1 percent of full scale. Provision is made for operation of a Clary printer and IBM summary punch from the voltmeter output. (Non Linear Systems, Inc., Dept. S482)

■ MASS SPECTROMETER is a portable instrument for the mass range from 2 to 80. Resolving power is adequate for separation of adjacent peaks up to about mass 35. The scanning operation of the spectrometer causes mass numbers to appear uniformly spaced on a time base. A manual override permits rapid setting to any mass number. (Consolidated Electrodynamics Corp., Dept. S476)

■ IMPEDANCE BRIDGE measures capacitance, inductance, and resistance. For d-c resistance measurements, a built-in generator furnishes either 10 or 300 v to the bridge. Bridge null is detected by a light-beam galvanometer. For a-c measurements, a 0- to 15-v supply, operable from 100 cy through 10 kcy/sec, is used. Bridge null for alternating current is

indicated by an electron-ray indicator tube. Accuracies are: ± 0.1 percent for 0.1 mohm to 1.2 Mohm, ± 0.2 percent for 0.1 to 1200 μf, and ± 0.3 percent for 0.1 μh to 1200 h. (Electro-Measurements Inc., Dept. S527)

■ X-Y RECORDER draws curves in Cartesian coordinates. The unit has a sensitivity of 10 mv/in. Input resistance is 10,000 ohm. Writing speed is 7.5 in./sec on standard 8½- by 11-in. graph paper. (Mandrel Industries, Dept. S464)

■ AUTOMATIC BLOOD ANALYZER determines urea and sugar in blood and calcium in serum. The samples to be analyzed are picked up by a tube from a rotating sample plate. Reagents are added by a proportioning pump. Diffusible constituents are removed by a dialyzer. Measurements are made by a photoelectric colorimeter and recorded graphically. (Technicon Company, Dept. S468)

■ PULSE TRANSFORMER KIT consists of 5 subminiature, metal-cased, hermetically sealed pulse transformers. The transformers measure ½ in. in diameter by ⅜ in. in length. Ferrite toroidal cores are used. (CBS Electronics Co., Inc., Dept. S478)

■ SAMPLING SWITCH has two poles and 30 contacts per pole, providing 60 channels in make-before-break operation. A filtered 27.5-v d-c motor rotates the switch at 2.5 rev/sec. (Applied Science Corp. of Princeton, Dept. S479)

■ LOW-PASS FILTERS are available for standard cutoff frequencies of 7, 20 and 40 kcy/sec. Attenuation is 1 db at the cutoff frequency and 12 db per octave at higher frequencies. Input impedance is 500 ohm, output impedance 4000 ohm. (Flow Corporation, Dept. S494)

■ VACUUM SYSTEM produces ultimate vacuum of 1.8×10^{-7} mm-Hg with liquid nitrogen trapping. Valves, controlled by lever operation, can be set to close automatically in case of vacuum failure. Both the high-vacuum and forepump pressures can be measured. The entire system is mounted on casters with jackscrews, adjustable from the top, for immobilizing the unit. (Scientific Engineering Laboratory, Dept. S497)

■ DIFFERENTIAL TRANSFORMER KIT consists of seven differential transformers having linear displacement ranges from ± 0.01 to ± 2.5 in., a flexure plate and clamp for positioning coils, and a demodulator which converts the a-c output of the transformer into d-c voltage. (Automatic Temperature Control Co., Dept. S498)

JOSHUA STERN
National Bureau of Standards

PERSONNEL PLACEMENT

CLASSIFIED: 18¢ per word, minimum charge $3.60. Use of Box Number counts as 10 additional words.

COPY for classified ads must reach SCIENCE 2 weeks before date of issue (Friday of every week).

DISPLAY: Rates listed below — no charge for Box Number. Monthly invoices will be sent on a charge account basis — provided that satisfactory credit is established.

Single insertion	**$22.00 per inch**
13 times in 1 year	**21.00 per inch**
26 times in 1 year	**20.00 per inch**
52 times in 1 year	**19.00 per inch**

For PROOFS on display ads, copy must reach SCIENCE 4 weeks before date of issue (Friday of every week).

Replies to blind ads should be addressed as follows:
Box (give number)
Science
1515 Massachusetts Ave., NW
Washington 5, D.C.

POSITIONS WANTED

Bacteriologist, Ph.D., with broad experience wishes change of academic position. Box 232, SCIENCE. X

Biochemist, Ph.D.; 3 years, full-time university teaching; 6 years, director, research, well-known institution; recognized as authority in field of steroid analysis. Medical Bureau, Burneice Larson, Director, 900 North Michigan Avenue, Chicago. X

POSITIONS OPEN

(a) Analytical Chemist and Biochemist, Ph.D.'s, to direct groups, new research center, large industrial company; Pacific Coast. **(b) Toxicologist;** although Ph.D. in pharmacology preferred, one with doctorate in biochemistry acceptable; industrial toxicology laboratory, large company; experience in industrial toxicology advantageous; $10,000; East. **(c) Medical Director;** preferably one who completed training at least 5 years ago; duties: professional correspondence, lecturing, technical consultation, supervising clinical studies; important pharmaceutical company; university city, West. **(d) American Professors in Anatomy, Pharmacology, Biochemistry,** and **Pathology** to develop departments, postgraduate institute, foreign medical college; openings, also, for **Assistant Administrator** and **Medical Librarian;** transportation, homes provided; 2-year contracts. **(e) Microbiologist,** Ph.D.; duties principally research, supervising clinical diagnostic bacteriology, conducting tissue culture laboratory; research department, 600-bed hospital; $7000–$8000; East. S8-2 Medical Bureau, Burneice Larson, Director, 900 N. Michigan Avenue, Chicago. X

Bacteriologist to head division of bacteriology and serology in 450-bed hospital. Training in medical bacteriology preferred. Salary depends on experience and degree. Apply to Director of Laboratories, Good Samaritan Hospital, Dayton 6, Ohio. 8/2, 9

Biochemist, M.S., with experience in blood pigments. Full-time research; salary $5000–$6000; midwestern medical school. Send complete résumé. Box 226, SCIENCE. 8/9

Chemist. Teaching position in general chemistry, organic-biochemistry with some research opportunity. Salary ($5500 to $7500) and title depending upon qualifications and experience. Position is on a 10-month basis. Interview requested. Write details of training and experience to F. Reese Nevin, Chairman, Department of Science and Mathematics, State University Teachers College, Plattsburgh, New York. 8/2, 9

Clinical Chemist, with hospital experience preferred, for 450-bed hospital. Salary in range of $5000 and dependent on degree and experience. Apply to Director of Laboratories, Good Samaritan Hospital, Dayton 6, Ohio. 8/2, 9

Director, diagnostic and research tuberculosis laboratory, central Florida, physician or nonphysician microbiologist or clinical chemist. Part-time employment will be considered. Write Dr. Albert V. Hardy, Director, Bureau of Laboratories, State Board of Health, P.O. Box 210, Jacksonville, Florida. uc

POSITIONS OPEN

CHEMIST
BIO-ORGANIC

Large progressive North Jersey ethical drug research laboratory needs young doctorate level chemist with 3 to 5 years' experience in the isolation and characterization of natural products, especially ANTIBIOTICS and alkaloids. Should be familiar with modern analytical procedures. Supervisory potential important. In confidence please send curriculum vitae, including salary requirements, to Box 229, SCIENCE.

Clinical Chemist, M.A. or Ph.D. Starting salary $6000–$9000 depending on qualifications. To head chemistry department small progressive hospital in rural Connecticut. Write Dr. M. Z. Rosenberg, Pathologist, Windham Community Memorial Hospital, Willimantic, Conn. X

Editor, Assistant. Scientific publishing house. Unusual opportunity. Background in science helpful. No publishing experience necessary. Some traveling; headquarters New York. Send résumé, salary desired. Box 231, SCIENCE. X

Medical Technicians, General (male) for employment with U.S. Government. Under 38 years of age. Must be U.S. citizen. Military experience in medical field desirable. Knowledge of x-ray and laboratory procedures necessary. Willing to serve overseas. Beginning salary $4080 per annum plus allowances. We request that initial reply include professional background and military experience. Box 235, SCIENCE. 8/16, 23, 30; 9/6, 13, 20, 27

Microbiological Analyst needed. A bachelor of science in bacteriology with training in chemistry for full-time position, assisting with nutrition research. Write Professor M. L. Scott, Rice Hall, Cornell University, Ithaca, New York. X

Microbiologist. To head laboratory in Surgical Research Department. Dual appointment—Surgery and microbiology. Rank and salary depend on qualifications. Experience with clostridial toxins needed. Address Department of Surgery, Louisiana State University, School of Medicine, New Orleans, La. 7/26; 8/2, 9

PHYSIOLOGIST

Ph.D. required for high level position in basic research program devoted to the physiological and psychological phenomena accompanying sleep and wakefulness. This man must be a creative and energetic scientist, capable of leading and directing the work of physiologists, statisticians, and electronic engineers on a research program that has been in progress for more than 10 years. Salary open. Box CS 975, 125 W. 41 St., New York. X

Plant Physiologist, Ph.D., to work as member of a team on problems of soil moisture relations of crop plants. A full-time research position with government agency. Location at outstanding state college in Southeast with complete research facilities. College staff status. Entrance salary from $5440 to $7570, depending upon postdoctoral experience and qualifications. Experience and/or training in the work area is desirable. Write to Box 221, SCIENCE. 8/2, 9

SCIENCE TEACHERS, LIBRARIANS, ADMINISTRATORS urgently needed for September positions in many states and many foreign lands. No fees. Apply direct. Also study awards. Rush $1 for complete job data, salaries. CRUSADE, SCI, Box 99, Station G, Brooklyn 22, N.Y. EW TF

The MARKET PLACE

BOOKS • SERVICES • SUPPLIES • EQUIPMENT

DISPLAY: Rates listed below — no charge for Box Number. Monthly invoices will be sent on a charge account basis — provided that satisfactory credit is established.

Single insertion	$22.00 per inch
13 times in 1 year	21.00 per inch
26 times in 1 year	20.00 per inch
52 times in 1 year	19.00 per inch

For PROOFS on display ads, copy must reach SCIENCE 4 weeks before date of issue (Friday of every week).

BOOKS AND MAGAZINES

WANTED TO PURCHASE . . . **SCIENTIFIC PERIODICALS and BOOKS**

Sets and runs, foreign and domestic. Entire libraries and smaller collections wanted.

WALTER J. JOHNSON, INC.
111 Fifth Avenue, New York 3, New York

Your sets and files of scientific journals

are needed by our library and institutional customers. Please send us lists and description of periodical files you are willing to sell at high market prices. Write Dept. A3S, J. S. CANNER, Inc. Boston 19, Massachusetts

PROFESSIONAL SERVICES

TO AUTHORS
seeking a publisher

Learn how we can publish, promote and distribute your book on a professional, dignified basis. All subjects considered. Scholarly and scientific works a specialty. Many successes, one a best seller. Write for booklet SC—it's free.

VANTAGE PRESS Inc. • 120 W. 31 St., N.Y. 1
In Calif.: 6253 Hollywood Blvd., Hollywood 28
In Wash., D.C.: 1010 Vermont Ave., NW

LaWall & Harrisson SINCE 1870
Est. S. 1921 Walnut St., Philadelphia 3, Pa.
Food & Drug PROBLEMS
Pharmacological BACTERIOLOGICAL CHEMICAL

FOOD RESEARCH LABORATORIES INC.
OUR 35th YEAR
FRL
RESEARCH
ANALYSES CONSULTATION
BIOLOGICAL, NUTRITIONAL AND TOXICOLOGICAL STUDIES FOR THE FOOD, DRUG AND ALLIED INDUSTRIES
48-14 33rd STREET, LONG ISLAND CITY 1, N.Y.
Western Office—9321 VENICE BOULEVARD, CULVER CITY, CALIF.

"OUR PREVIOUS AD

created a great deal of interest, for which we are grateful. Additional advertising in your magazine is contemplated."

PROFESSIONAL SERVICES

WISCONSIN ALUMNI RESEARCH FOUNDATION

LABORATORY SERVICES
for the FOOD, FEED, DRUG and CHEMICAL INDUSTRIES
Analyses, Biological Evaluation, Toxicity Studies, Insecticide Testing and Screening, Flavor Evaluation.
Project Research and Consultation
Write for Price Schedule
P. O. Box 2217 • Madison 1, Wis.

SUPPLIES AND EQUIPMENT

PURINES C^{14}
and other tagged compounds
OF HIGH RADIOPURITY
ISOTOPES SPECIALTIES COMPANY INC.
703 S. Main St. Burbank, Calif.

ELLIPSOMETERS
for Thin Film Measurements.
O. C. RUDOLPH & SONS
CALDWELL, NEW JERSEY

Special LaMOTTE Reagents for Analysis

TIRON—for determination of Iron, Titanium, and Molybdenum

ZINCON—for determination of Zinc and Copper

★★★★

Send for LaMotte Catalog on CHEMICAL CONTROLS for
pH, Chlorine, Phosphates and Polyphosphates, etc.

LaMotte Chemical Prod. Co.
Dept. H Chestertown, Md.

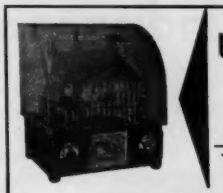
---

albino rats*
**Descendants of the Sprague-Dawley and Wistar Strains*
•
Hypophysectomized Rats
•

HENRY L. FOSTER, D.V.M.
President and Director
THE CHARLES RIVER BREEDING LABS.
Dept. B, Wilmington, Mass.

MICROSCOPES
SCIENTIFIC INSTRUMENTS
NEW AND USED
WE BUY, SELL & TRADE
Write us what you need and what you want to dispose of.
THE TECHNICAL INSTRUMENT CO.
122 Golden Gate Ave., San Francisco 2, Calif.

SUPPLIES AND EQUIPMENT



ULTRAMICRO
CONTINUOUS FLOW
KARLER-KIRK
ELECTROCHROMATOGRAPHY
KARLER-KIRK UNIT
....WRITE FOR DATA →
MICROCHEMICAL SPECIALTIES CO.

QUALITY SERVICE
SWISS WEBSTER MICE
BELLEWOOD FARM
ENGLISHTOWN, N.J. Ph. 7-9438

Palo
LABORATORY STIRRER Model #7605 D
$30. complete with 3 bladed propeller

Universal, low priced direct drive stirrer for general laboratory use. High quality, continuous duty motor; rheostat control—0 to 7,000 RPM ¼" true running chuck, 10 in. stainless steel rod.
WRITE FOR BULLETIN X-1
PALO LABORATORY SUPPLIES, Inc.
81 Reade St., New York 7

• HYPOPHYSECTOMIZED RATS
Shipped to all points via Air Express
For further information write
HORMONE ASSAY LABORATORIES, Inc.
8159 South Spaulding Ave., Chicago 29, Ill.

YOU can TELL and SELL more than 33,500 scientists here . . . at a very low cost.

Your sales message in an ad this size costs only $55.00 at the one-time rate—less for multiple insertions. And the results!—well, here's what one of the many satisfied advertisers in SCIENCE has to say . . .

"SCIENCE is consistently our most profitable medium. Business secured solely thru SCIENCE ads has been the backbone of our success in this field."

"We carry a considerable amount of advertising in various periodicals, but none is so productive of results as SCIENCE."

Prove to yourself the effectiveness of SCIENCE in increasing your Market, Sales and PROFITS—send your "Copy" NOW—or write for further information and Rate Card No. 29-A.

SCIENCE 11 West 42 St. New York 36, N.Y.

APPLICATION FOR HOTEL RESERVATIONS

124th AAAS MEETING

Indianapolis, December 26-30, 1957

The list of hotels and their rates and the reservation coupon below are for your convenience in making your hotel room reservation in Indianapolis. Please send your application, *not* to any hotel directly, but to the AAAS Housing Bureau in Indianapolis and thereby avoid delay and confusion. (Exception: Members of the American Astronomical Society who wish reservations at the Marott Hotel, 2625 North Meridian Street, are asked to correspond directly with that hotel.) The experienced Housing Bureau will make assignments promptly; a confirmation will be sent you in two weeks or less.

As in any city, single-bedded rooms may become scarce; double rooms for single occupancy cost more; for a lower rate, share a twin-bedded room with a colleague. Most hotels will place comfortable rollaway beds in rooms or suites at 2.50 to 3.00 per night. Mail your application *now* to secure your first choice of desired accommodations. All requests for reservations must give a definite date and estimated hour of arrival, and also probable date of departure.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Rates for Rooms with Bath

All hotels have sessions in their public rooms. For a list of headquarters of each participating society and section, please see *Science*, July 19, or *The Scientific Monthly* for August.

Hotel	Single	Double Bed	Twin Bed	Suite
Antlers	$4.50–10.00	$7.00–12.00	$10.50–12.00	$14.50–19.50
Claypool	7.00–10.00	9.50–14.00	10.50–14.00	13.50–34.00
Continental	8.00–10.00	8.00–12.00	8.00–12.00	12.00–15.00
Marott	7.00–14.50	9.00–14.50	10.00–17.50	14.50 and up
Severin	6.00– 9.00	8.50–12.50	11.00–15.00	25.00
Sheraton-Lincoln	6.50–11.50	9.85–15.00	13.35–16.00	24.35 and up
Warren	6.50–10.50	8.50–12.50	12.00–13.00	25.00–35.00
Washington	5.50–10.00	7.00–11.00	11.50–16.00	18.00–45.00

THIS IS YOUR HOUSING RESERVATION COUPON

AAAS Housing Bureau
1201 Roosevelt Building
Indianapolis 4, Ind.

Date of Application .....

Please reserve the following accommodations for the 124th Meeting of the AAAS in Indianapolis, Dec. 26–30, 1957:

TYPE OF ACCOMMODATION DESIRED

Single Room ..... **Desired Rate** ..... **Maximum Rate** .....

Double-Bedded Room ..... **Desired Rate** ..... **Maximum Rate** ..... **Number in party** .....

Twin-Bedded Room ..... **Desired Rate** ..... **Maximum Rate** .....

Suite ..... **Desired Rate** ..... **Maximum Rate** ..... **Sharing this room will be:**

(Attach list if this space is insufficient. The name and address of each person, including yourself, must be listed.)

.....

.....

First Choice Hotel ..... **Second Choice Hotel** ..... **Third Choice Hotel** .....

DATE OF ARRIVAL ..... **DEPARTURE DATE** .....
(These must be indicated—add approximate hour, a.m. or p.m.)

NAME .....
(Individual requesting reservation) **(Please print or type)**

ADDRESS .....
(Street) **(City and Zone)** **(State)**

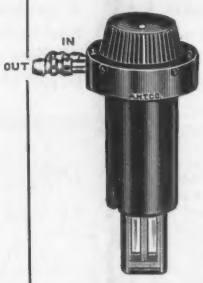
***Mail this now to the Housing Bureau.* Rooms will be assigned and confirmed in order of receipt of reservation.**

Thomas ACCESSORIES
for B. & L. "SPECTRONIC 20"
SPECTROPHOTOMETER-COLORIMETER

CELL CARRIER
for 0.4 ml sample

9085-D1.

ROTO-CELL
for 1 ml sample
and standard



9085-C.

DIDYMIUM FILTER
for Calibration

9085-W.

9085-D1. CELL CARRIER, Thomas, 0.4 ml, 10 mm light path. Permits use of sample as small as 0.4 ml in 9085-E Sample Holder (with spring on same side as cover hinge), which is regularly furnished with B. & L. "Spectronic 20" Spectrophotometer-Colorimeters 9084-A to 9084-K, inclusive. Takes 9085-N2 Absorption Cell, with 10 mm light path, as used in the Thomas Roto-Cell. By means of the precisely located window of the carrier, the light beam is reduced slightly in height and passes through the cell just above its bottom. This arrangement decreases the required sample size while retaining adequate energy for measurements. Constructed to ensure reproducible results by simply inserting carrier into sample chamber firmly so that the light shutter at bottom is completely opened. Made of nickel-plated brass, with handle at top and clip for retaining cell. Complete with Absorption Cell of Corex glass and Cover of polished plate glass.....**35.25**

9085-C. ROTO-CELL, Thomas, 1 ml sample, 10 mm light path, for rapid scanning. A liquid-cooled double cell carrier for rapid spectrophotometric scanning at controlled temperatures. Swivel action permits instantaneous interchange *within the instrument*, of a 1 ml sample and blank or standard into light path, facilitating preparation of spectral transmission or absorption curves. Readily interchangeable with standard single place sample holder. Water jacket type, brass housing has inlet and outlet tubulature to connect with external cooling system. Includes light proof collar, rotating cell carrier and control knob for positioning cell. Complete with Partitioned Cell of Corex glass, two Cell Covers, and directions for use.....**76.20**

9085-W. DIDYMIUM CALIBRATION STANDARD. For checking wavelength scale calibration and meter performance of B. & L. "Spectronic 20" Spectrophotometer-Colorimeter. Consisting of a Corning No. 1–60 didymium glass filter mounted in end of phenolic plastic holder, approximately 13 mm x 13 mm x 100 mm long. Window in opposite end of the holder provides unobstructed air path for light beam when holder is inverted, for setting meter reading at 100% transmittance. Standard fits directly into Sample Holder as supplied with "Spectronic 20." Complete with directions for use, including spectral transmission curve for the filter.....**9.00**

QUALITY AND SERVICE
A.H.T.CO.
PHILA. U.S.A.
LABORATORY APPARATUS

ARTHUR H. THOMAS COMPANY

More and more laboratories rely on Thomas / *Laboratory Apparatus and Reagents*

VINE ST. AT 3RD • PHILADELPHIA 5, PA.